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"The Pathology of Syphilis of the Nervous System in the Light of Modern Research."

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PATHOLOGY OF SYPHILIS OF THE NERVOUS SYSTEM IN THE LIGHT OF MODERN RESEARCH.

Mr. President and Fellows of the College: Allow me to thank you for the great honour of having been invited to give the Morison Lectures in this ancient College of a city, so long renowned as a great seat of medical science and learning.

In considering the general pathology of syphilis of the nervous system it is not necessary to refer to the different bacterial and other organisms which have been described by various authorities as being the specific agent in the production of the lesions characteristic of this disease before the discovery of the *Spirochæta Pallida* by Schaudinn. This organism, whether it be, as its discoverer believed, a protozoon or a bacterium or micro-organism between a protozoon and a bacterium, is regarded as the specific organism of syphilis by those best competent to judge, viz., Metchnikoff, Hoffmann, Neisser, Levaditi, Bertarelli, Shennan, and many others. Metchnikoff and Roux were the first to demonstrate experimentally the communicability of syphilis to animals and to show that the nearer the animal approached to man, the more the disease approached in its characters and virulence the human form of the malady. Thus, although other animals, especially apes and anthropoid apes, have been successfully inoculated, the chimpanzee alone reproduces with absolute certainty the human symptomatology. This is as we should expect, for the blood precipitin reaction of this anthropoid approaches most nearly that of man. The experiments of Neisser, Hoffmann, Bertarelli, Levaditi,

and numbers of others have confirmed this important discovery, and many new facts have been added to our knowledge of the general pathology of syphilis by experiments on apes and other animals, and I would mention in particular the important discovery by Bertarelli, who was able to inoculate the spirochaete into the cornea of the rabbit and transmit it through a series of such animals. Levaditi has experimented successfully with the cornea from one of these animals and not only transmitted it through a series of rabbits, but used the cornea infected with spirochaetes to produce an infection of the eyelid of an anthropoid ape. Lastly may be mentioned the important observations upon the biochemical changes in the fluids of the body by the Wassermann, Neisser Brück method of serum diagnosis. Upon this tripod, of the discovery of the specific spirochaete, the communication of the disease to apes and the serum diagnosis, a vast amount of most valuable work rests, the tripod is mutually supporting and every day fresh evidence is forthcoming to strengthen the opinion that the true cause of syphilis has been discovered; that, although as yet no vaccine has been successful, this is no longer a hopeless outlook; and, lastly, a most valuable means of diagnosis of syphilis and parasyphilis has been obtained.

The Microbiology of Syphilis.

The *Spirochæta Pallida* examined in fresh preparations is seen with much greater difficulty than other coarser spirochaetes which may exist in the primary sores on the genitals or secondary papules of mucous surfaces. Hoffmann states in order to find them, it is necessary to seek the edges of red blood corpuscles, to which they often are seen to be attached by one end (a process of chemotropism). It is barely $\frac{1}{4}\mu$ thick and possesses on an average 8-12 very regular, narrow, and very steep coils, the height of which at the ends diminishes somewhat. (*Vide* Figs. 1, 2, 3, 4, Plate I.) The length of this cork-screw-like organism varies within wide limits, from a few up to 26 coils or even more. Examined with a paraboloidal reflecting substage condenser, by which living organisms appear light on a dark background, the *Spirochæta Pallida* can be seen to rotate on its long axis and oscillate to and fro with a pendulum-like movement, contrasting thus with the coarser and larger spirochaetes, which have an eel-like movement. An observation of Hoffmann showed that the untreated serum of a syphilitic patient caused a cessation of movement after about a couple of hours.

DIFFERENCE BETWEEN THE SYPHILIS SPIROCHAETE AND OTHER KINDS OF SPIROCHAETES.—(*Hoffmann*).

Syphilis Spirochaete.	Other Forms.
1.—Large size 10–15 μ on the average, still often more than this. The extreme tenuity of the fibre ($\frac{1}{4}$ μ). This relation between length of fibre and its thickness is very characteristic.	1.—Fibres relative to their length far thicker, therefore they have a plumper appearance ; the finer forms are mostly shorter than the sp. pallida.
2.—Very slightly refractile in fresh preparations, therefore only visible with the best apochromatic lenses.	2.—Strongly refractile, and therefore easily seen in fresh preparations.
3.—Ends are pointed, often terminating in long red threads.	3.—Ends blunt. End threads seldom seen.
4.—Movements screw-like around this long axis ; lateral pendulum movements ; movements forwards and backwards still less active, often remains a long time inactive anchored to a blood corpuscle, whilst it exhibits rotatory and slight pendulum movements.	4.—Lateral movement much more active, eel like and sinuous, and more rapid change of position. Anchors to cells much less frequently, and detaches itself quicker.
5.—The spiral possesses deep, steep, and very regular coils of cork-screw form. Fibres excessively thin in comparison to the length and depth of the spiral.	5.—Coils flatter, irregular, in many forms (*Sp. Dentium*) narrower fibres, thick and plump in comparison to the breadth of the coils.
6.—Relation of the depth to the length of the coils mostly greater than 1, namely, 1·0—1·2 ; 1·0—1·5.	6.—The known relation is smaller than 1.
7.—Great elasticity and retention of the spiral form, therefore with more difficulty deformable.	7.—Softer and more pliable, therefore the form is more changeable.
8.—Only trifling variations in breadth in respect to the form ; only the length therefore, also the number of coils variable.	8.—Great variability, all transitions from small to large, from thick to thin examples.
9.—It is coloured by Giemsa red (general scattered chromidial substance).	9.—Colour more bluish red ; nuclear rod or rod nucleolus in plasma often demonstrable.

Schaudinn and Hoffmann were able to prove that the *Spirochæta Pallida* is found in all cases of syphilis and is never found in any other affections. They also discovered spirochaetes in fresh preparations not only on the surface of the chancres and papules, whether of the skin or mucous membranes, but also in the depths of the tissues and in the juice of enlarged inguinal glands of syphilitic cases. Metchnikoff, Roux, and Levaditi have demonstrated the presence of the spirochaetes in chancres on the face and penis of monkeys in association with other organisms; they also found the spirochaete in papules. Buschke and Fischer discovered spirochaetes in abundance in the liver and spleen of an infant affected with congenital syphilis, and Levaditi demonstrated numbers of

spirochaetes in the fluid contained in the bullæ of pemphigus occurring in a congenital syphilitic infant. Since then an ever increasing army of workers have, with a few notable exceptions (Saling Schulze), supported the discovery of Schaudinn. In fact, this organism has been shown in every possible lesion which is definitely syphilitic. In some cases they cannot be found in the primary sore unless a very careful search is made, and even then the search may not be successful. The same applies, with even more force, to the secondary eruptions.

The spirochaetes have been discovered in the capillaries of the skin and in the perivascular tissue. Although only occasionally found in the blood, the spirochaetes are more numerous in the lymph and lymphatic organs in general, and, according to Metchnikoff, their presence in lymphatic vessels may be said to be constant in syphilis, and it is at times possible to see a very large number in the perivascular spaces, although their number in the corresponding blood vessels may be exceedingly limited. I have examined a number of primary sores, mucous tubercles, and cutaneous papules sent to me from the Lock Hospital and in all cases smears have shown spirochaetes by the Giemsa method,* sometimes, however, only after long and diligent research. In one case of secondary papules I found the spirochaetes by Levaditi method,† although I was unable to find them in the blood (*vide* Fig 7, Plate I.). When the disease becomes generalised and there is a polyadenitis, the organism can be found in glands far removed from the primary lesions; thus Lewandowsky found spirochaetes in the juice of the epitrochlear gland. It is presumed that for a short time, perhaps some hours, the organisms remain in the lymph clefts and spaces of the tissues at the point of inoculation; there it multiplies, and in a short time extends into the lymphatics and produces microscopic changes, although microscopic changes are not visible. In confirmation of this it may be mentioned that Levaditi and Yamanouchi have inoculated the chimpanzee with syphilis, and at a time when the point inoculated did not show the slightest microscopic indication of primary syphiloma they were able to

* *Giemsa Method.*—Make a film by expression and expose immediately to osmic acid vapour for two minutes. Dry in the air; then place in solution containing one drop Giemsa stain to 1 cc. distilled water for several hours. Wash in water and decolourize in solution of 5 per cent. tannin for some minutes. Wash again in water, and finally in absolute alcohol.

† *Levaditi Method.*—The tissues are fixed in 10 per cent. Formol for 24 hours or longer, and then left overnight in 95 per cent. alcohol, after which they are placed in distilled water until the pieces sink. They are then placed in 1·5 per cent. solution $AgNO_3$ 90 cc., Pyridin 10 cc., for 2 to 3 hours at room temperature, and 3 to 5 hours in a dark oven at 45° to 50° C. The tissues are then directly transferred to a solution containing 85 cc. (4 per cent. Pyrogallic acid solution, 90 cc., acetone 10 cc.) and 15 cc. pyridin, in which they remain overnight. They are then washed in distilled water, hardened in increasing strengths of alcohol, embedded in paraffin and sections 5 μ to 10 μ in thickness cut. These are stained by Polychrome methylene blue and differentiated with dilute glycerine, ether mixture, or tannic acid solution. Other authors use 1 per cent. Toluidin blue or Iodine green.

detect an active pullulation of spirochaetes and specific histological changes. The same investigators have recently published some very interesting researches upon incubation in syphilis. These observers have conducted a series of observations on keratitis in the rabbit induced by introducing a small portion of an infected cornea into the anterior chamber of the eye and by killing the animals at varying periods of time afterwards. They have also introduced the infected cornea of the rabbit beneath the skin of the eyelid in apes and a chimpanzee, and examined the tissues of spirochaetes by the Levaditi method. They have formulated the following conclusions. The period of inoculation which precedes the manifestation of the primary syphiloma of the monkey and the specific keratitis of the rabbit is not due to the existence of an evolutional cycle of the **Treponema pallidum*. It corresponds to the slow but progressive histological lesions provoked by the pullulation of the microbe of syphilis. This pullulation is not marked at first, in consequence of a defective assimilation caused, on the one hand, by a change of medium, and, on the other, by the conditions which preside over the supply of nutritive materials. But, as soon as the vessels and new-formed cellular elements assure to the treponemes the nutritive principles of which it has need, the multiplication by the parasite becomes active, and puts an end to the period of incubation.

The organisms after local development at the point of inoculation in man and in the anthropoid ape soon reach the nearest lymphatic glands, where probably they again multiply in the lymph sinuses and spaces, setting up an adenitis; these changes may be biological, provoked by the organism for its perpetuation, and not, as taught, in the nature of a defence on the part of the tissues against the invasion by the organism. The living organism usually prevails and passes into the general lymph stream, causing polyadenitis and an infection of glands remote from the seat of inoculation. The organisms may thus find their way into the thoracic duct, and a general infection of the blood stream takes place, with the development of the secondary eruption (roseola). Moreover, a profound biochemical change occurs in the blood and fluids of the body (*vide* p. 18). Occasionally, as first pointed out by Lang, and as I myself have observed in several cases quite early in the disease, even before the primary sore is healed, symptoms pointing to meningitis may occur; also, as will be pointed out later, and which I have seen illustrated by many examples, the most severe and the most intractable cases of brain and spinal syphilis occur within the first twelve months after infection; it is quite probable that

* Some authors prefer this name to *Spirochæta Pallida*.

the meninges were infected at the time of the roseolar rash in some of these cases, but the symptoms occurring then were slight and overlooked. Not infrequently severe symptoms of meningitis have occurred within a few months of the primary sore. It is reasonable to suppose that if the spirochaete is the cause of the secondary cutaneous eruption by a sort of metastatic process in the skin capillaries, that the same may occur in the meninges. The following case reported by Gautier and Maloizel is interesting in this respect, and tends to support that conclusion. A young woman affected with secondary syphilis had seven successive attacks of cutaneous eruption, simultaneously with sudden fever, headache, stiffness of the neck, and vomiting, accompanied by lymphocytosis of the cerebrospinal fluid; a complex of symptoms of syphilitic meningitis. Again, Boidin and Weil have reported a most interesting case of a young man, aged 18, who had (1) a hard chancre in the middle of June; (2) headache the middle of July; symptoms of meningitis and lymphocytosis of cerebrospinal fluid August 5th; roseolar rash August 12th. Cure of the meningitis by inunction August 17th. (See also a case of mine, page 25.) It is a pity that some of the fluid of such cases was not used for experimental inoculation of an ape. So far only Hoffmann has succeeded in showing that the cerebrospinal fluid may be infective, for he has successfully inoculated a monkey with the cerebrospinal fluid obtained blood free and taken with all precautions from a man suffering with a papular syphilide. Neisser states that Dohio and Tanaka have found spirochaetes in the cerebrospinal fluid in the case of a patient with a papular eruption; a second examination, as well as one by Neisser himself, was unsuccessful. It may be that centrifuging a fluid of such low density would disintegrate such delicate organisms. Again, we know that it is not infrequently impossible, except by culture or inoculation, to find tubercle bacilli in the cerebrospinal fluid of tubercular meningitis. Until experimental investigations have been made with fluid obtained from early acute cases of syphilitic meningitis, the absence of the organisms upon microscopic examination and failure of experimental inoculation is no valid argument against their being the cause of the meningitis. It may be said that if the spirochaetes are the cause of the meningitis, they could be shown in sections or in films of the exudation. It is seldom that syphilitic meningitis is rapidly fatal, and cases would rarely come under early enough observation; moreover, not more than 1 or 2 per cent. of syphilised persons suffer with *obtrusive* symptoms of meningitis, and they seldom die in consequence thereof, and still more rarely do they die for at least some months after the onset of symptoms. I have been unable by the silver or Giemsa method to find spirochaetes in the exudation of typical cases of syphilitic mening-

itis. But I was unable to find trypanosomes in the similar cell infiltrations of the meninges and perivascular spaces of sleeping sickness although I have examined quite a thousand sections obtained from thirty cases. Yet, it cannot be doubted that the *Trypanosoma Gambiense* is the exciting cause of the meningo-encephalitis.

Syphilis is characterised by being an eruptive malady following the inoculation of the virus, presumably the spirochaete of Schaudinn, and by the possibility during the remainder of the life of the individual of fresh eruptions occurring in connection with the existence of the virus in the body. A blow may be followed by a gumma, or a syphiloma may occur spontaneously in any part of the body at any period of time after infection. Microscopic examination shows that essentially the same tissue reactions occur in these late manifestations of syphilis as in the primary or secondary stages. It is well known that tertiary lesions are, as a rule, non-infective; consequently, we should not expect to find the active agent, or what we believe to be the active agent—*Spirochæta Pallida*—except in a few instances, and then only in small numbers. This is actually what has occurred. For a long time attempts to prove the existence of the spirochaetes in tertiary lesions failed, and this led to the not unwarrantable view (which may be true) that the organism may exist in a latent and attenuated, possibly intracellular form, and it is possible that late manifestations may be the result in some cases of secondary lesions which have remained latent until raised into activity by some exciting factor, such as exposure to cold, trauma, and toxæmia —microbial or otherwise; for, at no period after infection may such syphilitic meningitis occur. On p. 46 I have described a case of congenital syphilis in which cerebrospinal meningitis occurred in a girl of 16. I was unable, however, to find spirochaetes, although the meningitis was very active and typically syphilitic in its histological character. It must be admitted that this is a part of the microbiology which is unsatisfactory. The spirochaete, however, has, in a few instances, been found in a gummatous tumour. Schaudinn found it in a gumma of the liver. Blaschko recently claims to have discovered spirochaetes in scrotal papules which occurred sixteen years after infection. Reuter and Schmorl claim to have found spirochaetes in syphilitic aortitis embedded in the proliferated intima between the fibrils, sometimes in places in which regressive changes are absent. Moreover, Benda claims to have demonstrated typical spiral, straight and granular forms of the spirochaetes in the external layer of the media, and still more in the connective tissue adjacent to a patch of syphilitic endarteritis. Just as there are, relatively, but few successful observations proving the existence of spirochaetes in tertiary lesions, so there are, relatively, few

successful experiments of inoculation of animals from tertiary lesions. Hoffmann has, however, succeeded in inoculating an ape from a gumma occurring in a man three and a half years after primary infection. It has already been stated that the *Spirochæta Pallida* is an organism between a bacterium and a protozoon, and in spite of the divergent views respecting the classification of spirochaetes, there are, in my judgment, more characters linking them to the protozoon than to the bacterium. The *Spirochæta Pallida* contracts, moves, and modifies its structure in a manner different to a bacterium. The appearance of resting forms is totally different, and they arise in a different manner to the spores of bacteria (Prowazek). Again, the clinical aspect of affection from spirochaete invasion differs from that of bacterial diseases, and conforms especially to certain trypanosome infections. There is a periodicity of the symptoms altogether unknown in bacterial diseases. But, what has struck me from my own personal experience and knowledge, is the great similarity of the histological lesions of the nervous tissues of chronic trypanosome infections, *e.g.*, sleeping sickness and dourine, to syphilitic and parasyphilitic lesions. (*Vide* Figs. Plates II. and III.). The universal perivascular infiltration of lymphocytes and plasma cells in the central nervous system was thought by Nissl and Alzheimer to be pathognomonic of general paralysis and syphilis, but I have shown that exactly the same occurs in sleeping sickness. In the *mal de coit* of horses an ataxic paraplegia occurs, and I have found posterior root degeneration and sclerosis of the posterior columns in five cases of dourine sent to me from the Imperial Bacteriological Institute of India by Dr. Lingard. In all chronic trypanosome infections, *e.a.*, sleeping sickness and dourine, I have found a marked hyperplasia of neuroglia, and in experimental sleeping sickness of apes, as I shall show you, this connective tissue hyperplasia preceded the perivascular infiltration. Thus we see that in both syphilis and trypanosome infections we have a hyperplasia of the fixed tissue cell elements, endothelial and conjunctival, with little or no polymorphonuclear reaction. Moreover, Spielmeyer has obtained by experimental trypanosome infection of dogs, a lesion of the posterior columns of the spinal cord simulating the ataxic lesion; he has also produced optic atrophy. Again, there is a similarity in the fact that lymphocytes and plasma cells are found in the cerebrospinal fluid of trypanosome diseases of animals and man, *e.a.*, sleeping sickness. Moreover, Levaditi has shown that, in point of view of sensibility in respect to hæmolysing poisons, blood corpuscles, spirochaetes and protozoa constitute a homogeneous group, and the spirochaetes correspond in this respect more to the protozoon than the bacteria.

The study of all these diseases is primarily biological. The conta-

gium vivum is a living organism whose activities, like that of all living organisms, are for self-preservation and the preservation of the species. The chemical toxin which the organism produces is to enable it to live and multiply. The spirochaetes consist of a viscid plasm covered with a membrane which serves as a means of osmosis. This osmotic membrane is a lipoid substance, like that which forms the membrane of the red corpuscles, and is sensitive to hæmolysing substances.

The fact that Castellani has discovered a spirochaete which he terms *Sp. Pallidula* in yaws is of importance in showing that a spirillary organism not quite morphologically identical with that of syphilis is probably capable of producing a chronic disease in many of its features not unlike syphilis. It might be argued that all the postulates laid down by Koch have not been fulfilled, and, therefore, that we have no right to claim that the *Spirochæta Pallida* is the specific organism of syphilis. Thus the organism, although it has been grown in celloidin capsules, has not been cultivated on an artificial medium outside the body, and the disease reproduced by injection of such a culture. But the same argument might be applied to certain established protozoal diseases, *e.g.*, malaria and sleeping sickness. Dourine may almost be regarded as the syphilis of equines, for it is characterised by an infective sore on the genital organs, affection of the nearest lymphatic glands, then infection of the blood stream followed by successive eruption of plaques; and, as in syphilis so in dourine and sleeping sickness, the juice of the lymphatic glands, in a condition of acute swelling, shows the specific organisms more readily than the blood films. The trypanosomes may disappear from the blood entirely, even without the administration of drugs, and reappear, giving rise to an irritating eruption of papules and fever, and the trypanosomes can be found in smears obtained by scarifying the papules more readily than from smears of the blood. This was demonstrated by Lingard in the case of *mal de coit* of horses, and by the French observers in a case of sleeping sickness. So, also, in syphilis I have been able to find an abundance of spirochaetes in the secondary papules of the skin, although I was unable to find them in the same cases in the blood films (*vide* Fig. 7, Plate I.). It is a remarkable fact that Neisser was unable to inoculate animals by injecting the virus into the blood or into the organs; success was only obtained by scarifying an epiblastic skin surface and rubbing in the virus. This is precisely the seat of eruptions and pullulation. It looks as if the organism, to perpetuate the species, must find its way out of the body in the way it came in. Sir Patrick Manson (Huxley Lecture) expressed the opinion that, by analogy, we must presume that all trypanosome diseases are carried by some biting insect which acts as alternate host. But dourine spreads in the same way as syphilis. It is quite

possible that the *Trypanosoma Equiperdum*, which differs very little from the *Trypanosoma Evansii*, may be this trypanosome which has acquired the habit of pullulation in the mucous cutaneous orifices, and when infection occurs, always tends to get back there. In syphilis the same habit may have been acquired. It is known that mucous tubercles and condylomata (secondary eruptions) are more infective than the primary sore, and contain immense numbers of spirochaetes. Similarly, upon reading Lingard's experiments, I find he mentions that the *Trypanosoma Equiperdum* was found in great abundance sometimes in the vaginal mucus when it could not be found in the blood. Again, he was more successful when he inoculated animals by scarifying the genitals and inoculating with blood from a papule or with vaginal mucus than when he injected the blood into animals. Those facts accord very much with Neisser's experiments, and would seem to indicate that a habit had been acquired by the *Trypanosoma Equiperdum* of developing in the mucous membrane of the genital organs and of using this acquired habit as the means of preserving the species.

Finally, the therapeutic agents, mercury and arsenic in the many forms employed, are specific for both trypanosome and spirochaete affections. They are not of much use for bacterial infections. Mercury, particularly in the form of inunction, is especially valuable, and this may be owing to the fact that it prevents the pullulation of the spirochaetes on the surface of the body, including the mucous orifices, a habitat which these organisms have found particularly favourable for perpetuation of the species by transmission to another individual. Mercury, moreover, administered in any way, tends to come out by the skin, as can be readily demonstrated.

I have pointed out that, practically, the morbid tissue changes in syphilis are similar, whether the lesion be the primary sore or a gumma twenty years later; moreover, it is difficult to understand how the spirochæte, seeing that is has hardly ever been found in tertiary lesions, can produce the same specific cell hyperplasia so long after the primary infection. The following hypotheses may be put forward to explain the phenomenon of a gumma appearing spontaneously in the central nervous system long after the primary sore and apparent cure of the disease:—

1. The spirochaete, or some modified form of it, has remained latent in the tissues at the seat of the lesion, and, for some reason, inherent or otherwise, the resistance of the tissues at that particular spot has become lowered, and the organism has exerted again its specific activity—possibly in some not yet discovered intracellular form.

2. The specific organism has remained latent in some other tissue, *e.g.*, the marrow of bone, the spleen or glands, and, escaping into the

blood or lymph circulation, has, like a new growth, engendered a metatasis, which has developed and increased, producing a hyperplasia of the fixed tissue cell elements conjunctival and endothelial.

3. There may be varieties of specific spirochaetes, one of which may have an elective affinity for the central nervous system, as we know the *Trypanosoma Gambiense* has. It is difficult to differentiate this trypanosome from other forms by morphological appearances (*vide* Figs. 4 and 5, Plate I.) ; how much more difficult would it be to differentiate varieties of *Spirochæta Pallida.*

4. The invasion of the body by the spirochaetes has altered the blood and lymph biochemically, so that the tissue reactions to all causes which would lead to injury may take on the specific character.

Thus a blow on the head, vascular-stasis, or some inherent weak spot may become the seat of a gummatous process. Although we are only beginning to unravel these biological problems, the evidence so far appears to be in favour of the fixed tissue cell hyperplasia with subsequent necrobiosis and fibrosis being a reaction to the influence of the specific organism. The fibrosis may be regarded as the attempt on the part of the tissues to repair the damage done in the struggle between the specific virus and the tissues; it is accomplished by the young connective tissue cells which have survived the fray; these are converted into fibroblasts and eventually into sclerous fibrous tissue. The amorphous caseous material is the residuum of the dead cells and organisms, especially the former, which, owing to the toxic influence of the virus and the cutting off of the vascular supply, have undergone nucleolysis and plasmolysis. The organisms, when found, are not discovered here when the struggle is past, but at the growing edge, where the new blood vessels and embryonic cell hyperplasia is most active; for it is here that the organism finds pabulum for its multiplication.

PLATE I.

FIG. 1.—*Spirochæta Pallida* in smear preparation of condyloma, stained by Giemsa solution Magnification 3,400.

FIG. 2.—Another portion of the smear showing appearances of two spirochaetes twisted around one another ; possibly this is the result of longitudinal fission. Magnification 3,400.

FIG. 3.—*Spirochæta Pallida* from smear preparation of mucous tubercle. Magnification 1,800.

FIG. 4.—Section of spleen from a case of congenital syphilis, stained by Levaditi method. Magnification 1,400.

FIG. 5.—Blood smear from a case of sleeping sickness, showing *Tryp. Gambiense.* Magnification 2,000.

FIG. 6.—Blood film showing *Tryp. Brucei.* Magnification 1,700.

FIG. 7.—Section, showing spirochaetes, of a papule of skin from a case of secondary syphilis, before mercury was administered. Stained by Levaditi method. Magnification 1,000.

It will be observed that it would be difficult to decide the nature of the two trypanosomes by morphological characters alone.

PLATE I.

FIG. 1.

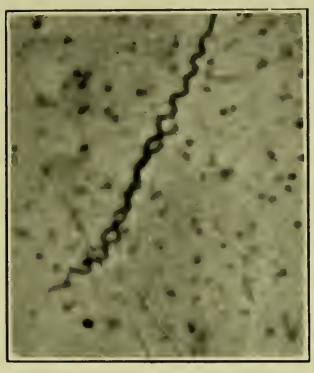


FIG. 2.

FIG. 3.

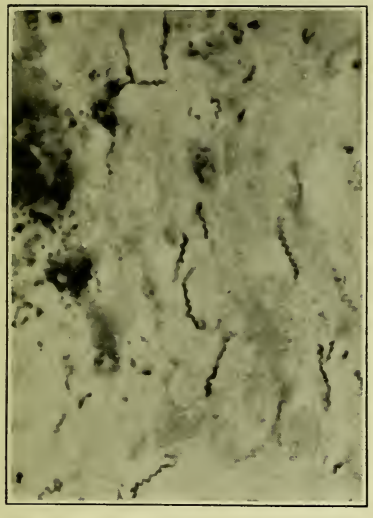


FIG. 4.

FIG. 5.

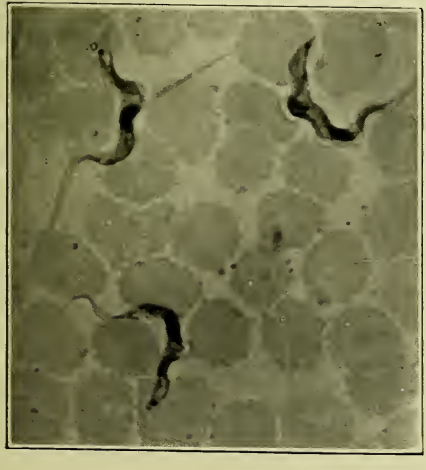


FIG. 6.

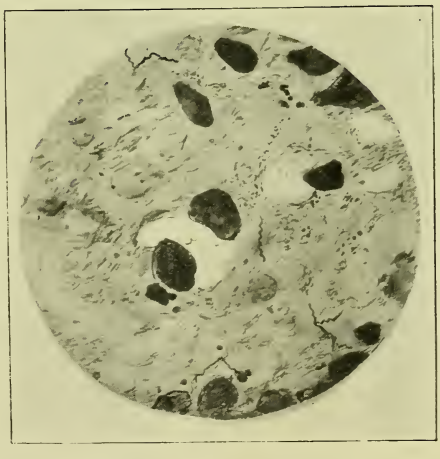


FIG. 7.

2-4—*Face p.* 12.

PLATE II.

FIG. 1.

FIG. 2.

FIG. 3.

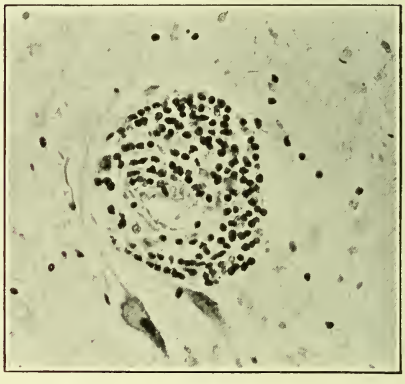


FIG. 4.

FIG. 5.

2–1—*Face p.* 13.

PLATE II.

FIG. 1.—Section of a small vessel showing the sheath infiltrated with lymphocytes and plasma cells, and with proliferated glia cells. Experimental sleeping sickness in an ape. Magnification 320. (Cf. Fig. 3, Plate III.)

FIG. 2.—Section of cortex cerebri from a case of sleeping sickness in a European. Stained to show the neuroglia. Magnification 450.

FIG. 3.—Section of brain of ape infected with *Tryp. Gambiense*, showing perivascular neuroglia cell hyperplasia. Below are seen a series of neuroglia cells in various stages of development. Magnification 320. (Cf. Fig. 4, Plate III.)

FIG. 4.—Perivascular infiltration with lymphocytes and plasma cells from a case of gummatous cerebrospinal meningitis. Stained by polychrome blue. Magnification 250.

FIG. 5.—Section of central nervous system from a case of sleeping sickness in a European, showing perivascular infiltration with lymphocytes and plasma cells. Magnification 250.

PLATE III.

FIG. 1.—Photomicrograph of a section of the ascending parietal convolution in a case of tabo-paralysis of four years' duration, showing a small vein surrounded by plasma cells, which are lying in a dilated lymphatic. The vessel at another part had ruptured and filled the lymphatic sheath with blood corpuscles. Some of the large swollen cells showed in their interior the blood pigment in various stages of destructive disintegration; they appear to have, therefore, a phagocytic function. Nissl stain. Magnification 500.

FIG. 2.—Section of syphiloma of the brain showing vessel with (*e*) thickened endarterium. (*l*) lymphocytes, (*p*) plasma cells. Magnification 300.

FIG. 3.—Section of small subcortical vessel, acute general paresis. (*l*) lymphocytes, (*p*) plasma cells. Magnification 300.

FIG. 4.—Small vessel, acute general paresis, showing neuroglia cells with proliferating nuclei and processes extending on to the small vessel. As in sleeping sickness there is little or no infiltration around because there is no pial or lymphatic sheath. Magnification 400.

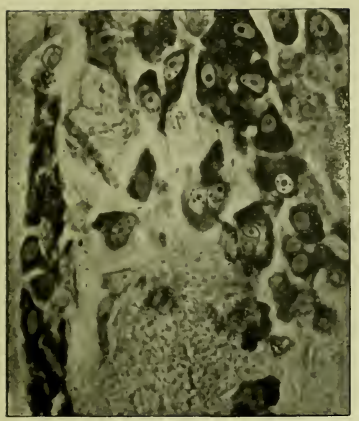


FIG. 1.

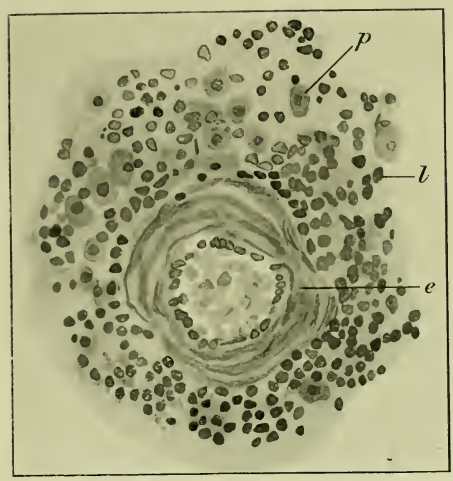


FIG. 2.

FIG. 3

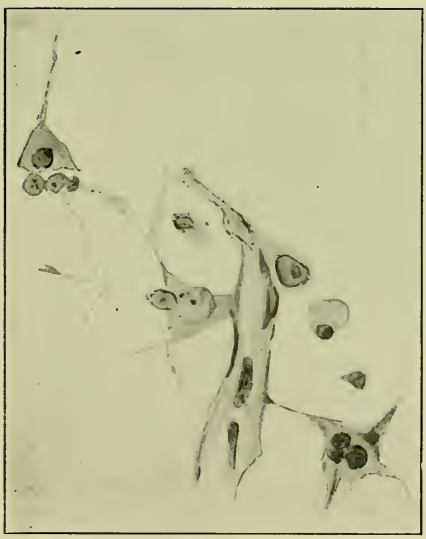


FIG. 4.

Lecture II.

In my last lecture I endeavoured to point out some facts and hypotheses of the biological problems of syphilis, especially in relation to disease of the nervous system. To-day I wish to draw your attention to modern researches bearing upon the bio-chemical changes which occur in the tissues and fluids of the body as a result of the entry and persistence of the syphilitic virus in the body.

I must, however, first make a slight digression, in order that you may obtain a better understanding of the altered bio-chemical conditions; this digression refers to the nature of lipoids, substances which have recently, in connection with hæmolysis, attracted a great deal of attention (and I wish here to acknowledge my indebtedness to Dr. Rosenheim for valuable information). "There seems to be a good deal of truth in the opinion of Bang that the importance of protein as carriers of life ("Träger des Lebens") has been over-estimated, while that of the lipoids has been neglected." Pflüger, and most physiologists, have taught that the vital activities depended essentially upon proteins. Bang contested this exclusive view. The name lipoid was given by Overton to *fat-like* substances which are contained in the cells of all living things, animal and vegetable. They were named by Waldemar Koch, lecithans, but this name has not been adopted. These lipoids may be divided into three groups (1) N. and P. free Cholesterin, fatty acids, and lipochromes; (2) Nitrogenous but P. free Cerebrosides; (3) Phosphatides containing both N. and P.; of these, the most important are the mono-amino phosphatide *lecithin* and the di-amino-phosphatide *sphingomyelin*.

These lipoids were, until recently, considered of little importance; in fact, cholestrin was looked upon as a physiological curiosity by virtue of the fact that its crystals had a chip out of one corner, and little else was said about it except that it was contained in the red blood corpuscles and formed the principal constituent of gall-stones. Lecithin was known to be a constituent of the red corpuscles, but it was not until Flexner and Noguchi's experiments on cobra venom had been published that the importance of these bodies in the action of toxins aroused attention. They found that cobra venom contains two poisons, a neuro-toxin and a globulin which has the property of dissolving red corpuscles. If, however, they washed the red corpuscles free of serum, the cobra venom no longer had a hæmolysing action; but, on adding serum to the washed corpuscles, an addition of the cobra venom produced hæmolysis. Clearly something was contained in the serum which interacted with the venom to produce the result. Kyes showed that the activator is soluble in alcohol and in ether, and he finally identified the substance as lecithin. But cholesterin, another

lipoid, has the property of counteracting the activating effect of lecithin on cobra venom. This antagonism of cholesterin and lecithin points to some bio-chemical or bio-physical relationship between the two bodies. Moreover, this relationship as regards osmotic membranes and hæmolysis has been experimentally put to the test by Panucci. This observer constructed glass cells covered with a membrane impregnated with lecithin and cholesterin; in these he placed hæmoglobin solution and then suspended them in the toxin solution; the hæmoglobin behaved differently

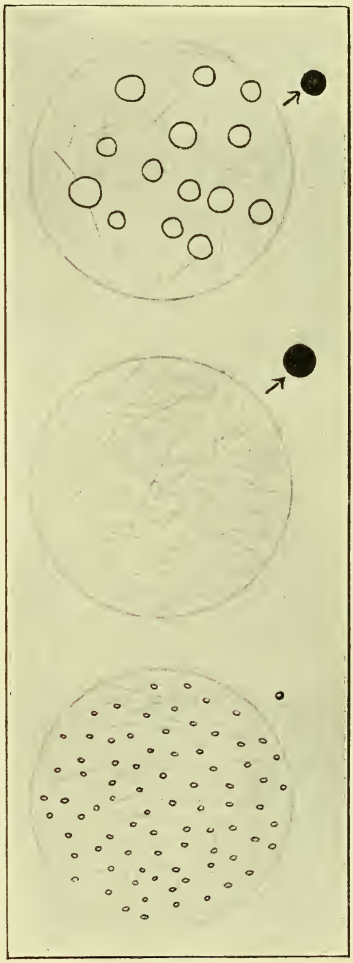


FIG. 1.

(*a*) Normal blood corpuscle with osmotic membrane permeable to ions of Na, K, Ca.
(*b*) Chemical explanation of hæmolysis by dissolution of osmotic membrane and escape of hæmoglobin.
(*c*) Physical explanation of hæmolysis by a bio-physical alteration of the osmotic membrane, by which it becomes permeable to the large hæmoglobin molecules.

(as regards diffusion) according to the proportions of these substances in the membrane. If we regard the red blood corpuscles as consisting of a sponge-like protein stroma holding the hæmoglobin in solution, the whole being covered with a membrane consisting of a properly adjusted complex of the lipoid substances, cholesterin and lecithin, then we may suppose that hæmolysis occurs as a result of a chemical or physical disturbance of the balance between the cholesterin and lecithin. In hæmolysis the membrane is either dissolved by the action of a ferment or a physical change occurs in the membrane, by which it becomes permeable to the large hæmoglobin molecules, whereas in its natural perfect state it will only allow the smaller ions, Ca, Na, and K, to pass through. (Fig. 1.) It is probable that all cells and unicellular organisms possess similar osmotic membranes, and that the lysis of these organisms depends upon physical or chemical changes, in the osmotic membrane which is termed a periplasium. The importance of this question is obvious in regard to cytolysis, bacteriolysis, and protozoolysis, and it will become especially apparent when we come to the study of the Wassermann reaction of the deviation of the complement in the sero-diagnosis of syphilis.

In regard to the origin of lipoids, especially in pathological conditions, it is necessary first to refer to an important paper by Munk just published. This observer has used the polarising microscope to distinguish between fat and lipoids in cells; the latter are doubly refractile when the Nicol's prism is rotated. Ambrose and Held made use of this method for determining the existence of the myelin sheath in the anterior and posterior roots of the embryo. Munk finds that the existence of lipoid droplets in the cell is associated with dissolution of the nucleus and destruction of the cell. Rosenheim remarks that the phosphatides may form a link with the cell nuclein which possibly obtain their necessary supply of phosphorus from this source. A lipoid substance in great abundance, then, means cell dissolution; the nucleus highly charged with phosphorus and the cell protoplasm break up into a lipoid complex as a result of the nucleolysis and plasmolysis. It may be suggested Levaditi's experiments show that the spirochaetes stimulate the fixed tissue cells to proliferate, and then, invading this bed of young cells rich in nuclein, they, by the action of some secretion or otherwise, cause these same embryonic cells to undergo lysis, thus providing the necessary pabulum for their own growth and proliferation. It is probable these young cells are more easily attacked than the older cells, and this may be the reason that the spirochaetes are found in such great abundance in fœtal tissues, and why the fœtal tissues, especially the liver, contains such an abundance of lipoid substance serving for the Wassermann reaction, although chemi-

cally it does not differ from lipoid substance which can be obtained from normal tissues.

We are now in a better position to consider the serum diagnosis by the Wassermann and other methods dependent upon bio-chemical changes induced in the body by the introduction of the syphilitic virus whereby immunity to future inoculation is effected; and which, in my opinion, lies at the root of the late degenerative processes occurring in the central nervous system, and which are collectively termed parasyphilitic.

Although it has now been ascertained that the syphilitic virus induces in the body metabolic changes whereby larger amounts of lipoids occur in the serum, and also in the cerebrospinal fluid in general paralysis and tabes, yet these same lipoids are found in the normal tissues and fluids, the specific character is manifested by quantity rather than quality. The substances which in hæmolysis play the part of *antigens* are lecithins, combined with other substances, especially soaps (Rondoni and Sachs), and those which play the part of *antibodies* are possibly complexes of lipoids and globulins. Yet, although in describing the Wassermann and other methods and the evolution of the knowledge concerning the same the terms antigen and antibody will be used, it is better to state at once that they do not conform to the antigen and antibody of bacteriolysins, and that the deviation of the complement (or fixation of the complement) may possibly depend upon the presence of those two kinds of lipoids, which we have previously seen play such an important part in the action of cobra venom.

The Serum Diagnosis of Syphilis by the Wassermann Method.

To explain the principles of this method it is necessary to make a few introductory remarks regarding its origin. Bordet, in 1901, discovered the phenomenon known as the absorption or deviation of the complement. At about the same time Gengou discovered a similar phenomenon when working with precipitins. Wassermann, Neisser and Brück, Levaditi, Citron, Plaut, Stertz and others have applied this method of the absorption of the complement of Bordet and Gengou to the diagnosis of syphilis by the existence of syphilitic antibodies and antigens in the blood serum and cerebrospinal fluid of persons suffering with primary, secondary and tertiary syphilis, as well as in the post-syphilitic, parasyphilitic (or late syphilitic) affections, viz., tabes and general paralysis. The epoch-making experiment of Pfeiffer on bacteriolysins may be said to have afforded the foundation of our knowledge of the principles governing immunity. Bordet, by his observations, came to the conclusion that bacteriolysis by the serum of an immunised animal was due to the presence of two substances, the one destroyed by heat (thermolabile)

present in normal serum, the other (thermostabile) a substance which resisted heat (56° C.) and was only present in the body fluids and blood of an immunised animal. The former is called the cytase or complement, the latter the immune body or antibody (amboceptor, Ehrlich).

Bordet and others, by experiment, found that if the corpuscles of one animal were injected into another of a different species, these corpuscles disappeared with the production in the serum of a specific hæmolysin analogous to the bacteriolysin; the hæmolytic properties of the serum being due to a specific antibody (immune body) linking up the cytase or complement to the corpuscles. This important discovery led to the possibility of the study of the theory *in vitro* and its practical application to the diagnosis of disease. The same principles determine the production of hæmolysins as bacteriolysins, and the solution of experimentally sensitised corpuscles can be used as a precise index of the presence or absence of one of the two unknowns, viz.: (1) the antigen: (2) the antibody or immune body. The thermo-labile substance cytase (Bordet) complement (Ehrlich) is contained in normal serum. Bordet holds that there is only one complement in normal serum, and, contrary to Ehrlich, that it is not a specific substance for each antigen, but specific for each animal. Bordet has introduced the terms antigen and antibody, the former to signify any substance which, when injected into an animal, will cause the production of an immune serum; the latter to denote the antagonising substance produced and which is the essential for the immunising action of the serum. Now, if either the antibody or the complement be not present, or be removed, the specific bacteriolytic or hæmolytic action of the serum or fluid is lost. Again, if the antibody in the presence of the complement is linked up to the antigen, both the antibody and the complement will be inactivated. To find out if a given serum or fluid, *e.g.*, cerebrospinal fluid, contains either the antigen or the antibody is by the experimental inductive method known as the *deviation of the complement.* How is this effected?

We require first to immunise an animal against the blood of some other animal; for this purpose the blood corpuscles of a sheep are injected into the circulation of a rabbit. The blood serum of the rabbit is thus made hæmolytic to the corpuscles of the sheep by virtue of an immune body *plus* the normal complement or cytase. The latter can be removed by heating to 56° C. for 30 minutes without destroying the former. We have thus the immune body, which by itself will not dissolve the washed corpuscles of the sheep. If, however, we add the normal serum of a guinea pig, the amboceptor or immune body links up the complement or cytase and the corpuscles are dissolved.

The second part of the experiment is the deviation of the complement or its neutralisation, so that hæmolysis no longer takes place when the serum of the guinea pig is added to the immune body and the washed sheep's corpuscles. This is effected by the presence of both antigen and antibody in the fluid to be examined. The serum, or cerebrospinal fluid, to be examined is mixed in varying dilutions with a watery (or alcoholic) solution of the liver of a syphilitic fœtus, which will contain the antigen (lipoid). A small amount of the serum of a guinea-pig is then

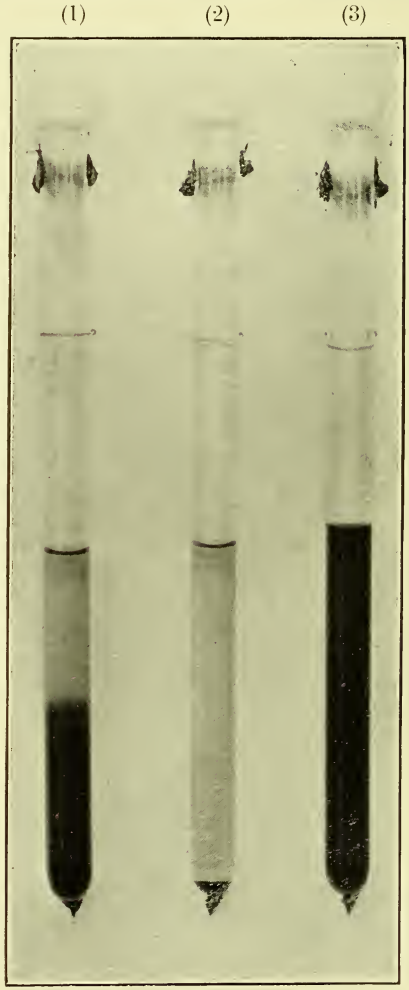


FIG. 2.

(1) Cerebrospinal fluid of general paralysis showing the Wassermann reaction on removal from the incubator.
(2) Ditto, after standing overnight on ice.
(3) Control with normal cerebrospinal fluid, showing total hæmolysis.

added and the total volume made up to 2 cc. with saline solution. The series of tubes containing these mixed solutions are placed in an incubator at 37° C. for one hour, and then the sensitised blood corpuscles are added. (By sensitised corpuscles I mean washed sheep's corpuscles in immune rabbit's serum which has been heated.) The mixtures are again placed in the incubator for two hours at 37° C., then taken out and put on ice over night. The next morning the amount of hæmolysis in each tube is estimated (*vide* Fig. 2). If, on the one hand, antigen and antibody have been present they have united with the complement, and no solution of corpuscles will have taken place because the complement is fixed; if, on the other hand, the immune body (antibody) was not present then the complement (cytase) has remained free to act upon the sensitised corpuscles and lead to their solution. A control experiment, using a normal serum, or cerebrospinal fluid, viz., one which contains no antibody, must be used at the same time.

In the hands of nearly all trustworthy and experienced investigators this method introduced by Wassermann has yielded most valuable results as a means of diagnosis. It is claimed even that it is more reliable than the Widal reaction for typhoid. Plaut obtained a positive reaction in 80 to 90 per cent. of undoubted cases of syphilis by this method. He found the reaction specific; it is not definitely present in a non-syphilitic individual; it enables a diagnosis of the constitutional disease to be made but not of the organ affected. He did not obtain the reaction with the cerebrospinal fluid in 25 cases of syphilis in which the nervous system was not affected, while the serum as a rule gave a positive reaction. This was not to be expected from what has already been said as regards the cerebrospinal fluid and its secretion. It shows that the reaction depends upon the production of some substances by the tissues of the nervous system themselves. The nature and origin of that substance will be discussed a little later, but reference will now be made to the remarkable unanimity of opinion of all those who have made experiments upon this subject as to the almost certainty with which the cerebrospinal fluid of general paralytics and, to a less degree, tabetics give this Wassermann reaction. According to Plaut the reaction may be negative with the cerebrospinal fluid in cases of syphilis of the nervous system, but he obtained a positive result in 94 out of 95 cases of general paralysis with the cerebrospinal fluid, and in every one of the cases the serum gave a positive reaction. In cases of cerebral syphilis the serum was usually positive and the cerebrospinal fluid usually negative; in 70 to 80 per cent. of the cases of tabes the cerebrospinal fluid gave a positive reaction. Citron, G. Meier, W. Fischer and G. Meier, Michaelis, Weygandt, Fleischmann and W. J. Butler and others have obtained similar positive results by

this method. At my suggestion, my assistant, Dr. Candler, in conjunction with Dr. Henderson Smith, of the Lister Institute of Preventive Medicine, has been engaged in applying this reaction to a number of my cases in the hospital and the asylums, with the following results:—

They have now examined the cerebrospinal fluid of 100 cases, of which 94 were asylum cases and six were in general hospitals. Forty-six cases of general paralysis were examined, 41 of which gave a positive reaction by the Wassermann test, a percentage of 89·1. The reaction was not obtained in any of the control cases. Two cases of locomotor ataxia failed to give the reaction, but it may be noted that neither was in an active stage. A negative reaction was also obtained in a case of syphilitic meningitis in which the cell contents of the cerebrospinal fluid were diminishing rapidly in numbers under specific treatment. It is also interesting to note that cases of tubercular meningitis failed to give the reaction, although in one case the cerebrospinal fluid contained a large number of leucocytes per cubic millimetre (*vide* Table).

AN ANALYSIS OF THE RESULTS OF THE WASSERMANN-PLAUT REACTION ON THE CEREBRO-SPINAL FLUID OF 100 CASES.

Table I.—Showing the Results of 94 Asylum Cases.

	No, of Cases.	Wassermann. +	Wassermann. —	Percentage of, + reaction.	No. of cases confirmed by autopsy.
Total number of cases of—					
General Paralysis, examined during life ...	42*	37	5	88·9 %	4†
(?) ,, ,, ,, ,, ...	6	—	6	—	—
Non-General paralysis ,, ,, ...	16	—	16	—	—
Locomotor ataxia ,, ,, ...	2	—	2	—	—
Insanity, examined during life (by lumbar puncture)	66	—	—	—	—
General paralysis (post mortem)	4	4	—	100 %	—
Non-General ,, ,, ...	24	—	23, 1 doubtful	—	—
Total number of cases examined—					
Post mortem	28	—	—	—	—
During life and post mortem	94	—	—	—	—
Total number of cases of general paralysis, examined during life and post mortem ...	46	41	5	89·1 %	—

* In six of the above 42 cases of G.P.I., the serum obtained from the blood, withdrawn during life, gave a positive Wassermann reaction.

† The C.S.F. of the four cases examined (post mortem), gave a similar result with the Wassermann Test as during life.

Table II.—Showing the Results of 6 Control Hospital Cases.

No.	Institution	Nature of Case.	Wassermann reaction.
1	Charing Cross Hospital... ...	Tubercular Meningitis. (P. M.)	—
2	„ „	Cerebellar tumour (totally blind.) (P. M.)	—
3	„ „	Syphilitic meningitis—	—
		1st examination, cell count 70 per 1 c.m.	
		2nd „ „ „ 20 „	
4	Victoria Hospital for Children...	Tubercular meningitis	—
5	„ „ „ ...	„ „	—
6	Charing Cross Hospital... ...	„ „	—
			—
		(1 c.m.=100 leucocytes, 8% lymphocytes).	

I wish here to acknowledge the kind assistance which has been rendered during this research by Dr. Robert Jones, the Medical Superintendent, and Dr. Hughes, Medical Officer of the London County Asylum at Claybury; Dr. Bond, the Medical Superintendent of Long Grove Asylum ; Dr. Ingram and other medical officers of the London Infirmaries; Mr. Gibbs, Surgeon at the London Lock Hospital; and Dr. Nepean Longridge, of Queen Charlotte's Lying-in Hospital for Women.

For the purpose of diagnosis, therefore, especially of general paralysis (Fig. 2), it is a very important addition to clinical methods. Since its application, however, many doubts have been cast upon the interpretation of the facts whether indeed the reaction is in any way due to syphilitic antibodies.

Levaditi and Yamanouchi made a study of the diagnosis of syphilis and general paralysis by the Wassermann method. The results of their researches are very favourable from the clinical diagnostic point of view. Levaditi and Marie have demonstrated the facts that normal liver can replace the syphilitic liver in the preparation of the antigen, and the cerebrospinal fluid of general paralytics supposed to be rich in antibodies is devoid of spirillicide properties. These facts show that the sero-reaction in question, although clinically a specific test for syphilis, had nothing to do with syphilitic antigens and antibodies. Moreover, the active substances of liver extract, syphilitic or normal, contrary to the true antigens, are soluble in alcohol; and the sero-reaction can be obtained with bile salts and with lecithin, or with soap (Sachs and Altmann), cholesterine and vaselin (Fleischmann), although more feebly. The sero-reaction of syphilis and of general paralysis is the same, and is not due to the intervention of antibody or syphilitic antigen in the usual sense of the word, and has no relation with the *Spirochæta pallida*. Landsteiner and Porges have also demonstrated that the extract of the liver

owes its particular properties for this reaction to the presence of lipoids and bile salts soluble in alcohol at 80° C. These products are found not only in the liver but also in different organs of man and animals. Landsteiner, Müller and Potzl state that in syphilitic serum substances are present which in the general sense are not anti-syphilitic bodies but which bind up with certain constituents of normal and syphilitic tissues. Moreover, they assert that the blood serum of animals infected with *Tryp. equiperdum* and *Tryp. Gambiense* contain similar substances which they have called *histaffines*. Yet being a characteristic reaction, it is attributable to the presence in the serum and in the cerebrospinal fluid of certain at present unknown compounds, which in the presence of bile salts, soaps and lipoids of the liver precipitate and determine the fixation of the complement. Levaditi and Yamanouchi consider that these compounds arising in the organism itself may be a cholesterin ester. Thus it will be seen that these authorities give a new interpretation to the phenomena of the Wassermann method, which, however, in no way militates against its value as a practical method of diagnosis.

They also assert that there are between normal serums and lipoids of the body and specific serums and liquids, only quantitative and not qualitative differences; the reaction of Wassermann is provoked by histogenic and not bacterial substances. They find, moreover, that lipoids serving for sero-diagnosis not only exist in the liver but in other organs, the brain, the corpuscles of the blood, etc. They are probably complexes in which lecithin largely enters into the composition.

Levaditi, Ravaut and Yamanouchi have proved that when syphilis leaves intact the central nervous system, although the serum gives a positive reaction the cerebrospinal fluid does not, and this is what one would expect. It is, however, different when the central nervous system is affected even in a slight degree. The cerebrospinal fluid can then acquire properties which enable it to yield the Wassermann reaction. In fact, in the four cases out of the many examined presenting nervous symptoms, which were neither tabetics nor paralytics, the fluid has twice given a positive reaction, although quite feeble. The method of fixation of the complement would up to a certain point then serve for the early diagnosis of syphilis, especially when the brain is affected.

The researches of the above-named authors show that there is not any parallelism between the results furnished by the cytological examination and those obtained by the Wassermann method. The leucocyte reaction may be very marked in certain secondary specific cases without the cerebrospinal fluid being in the least able to fix the complement. Such was the case in one of my patients with well-marked syphilitic cerebrospinal meningitis. This patient was a woman, aged 34 years,

admitted, under my care at Charing Cross Hospital, as a case of tabes. Upon examination I diagnosed cerebrospinal syphilitic meningitis (pseudo-tabes). Lumbar puncture was performed, and the fluid was found to contain 370 lymphocytes per cubic millimetre; she was put on mercurial inunction, and in a fortnight she had greatly improved. The lymphocytes were now only 70 per cubic millimetre; a fortnight later the lymphocyte count was 20 per cubic millimetre, and she was well enough to be discharged, nearly all the symptoms having disappeared. The Wassermann reaction was negative on the last two occasions, when lumbar puncture was performed; it was not tried in the first instance. The existence of numbers of lymphocytes in the spinal canal does not necessarily entail the appearance of substances which in the presence of lipoids engender the phenomenon of Wassermann. Marie and Levaditi found that there is a parallelism between the rapidity of progress of general paralysis and the degree of intensity of the Wassermann reaction, with which observations the results of Drs. Henderson Smith and Candler are in agreement; no doubt, therefore, there is a connection between the breaking down of nervous substances (destructive metabolism) and the amount of this complex lipoid substance, with which probably the reaction is associated and upon which it in a measure depends. I have been attempting to ascertain the chemical nature of this substance but my results are not yet sufficiently advanced to make any definite statement. However, I have found that the blood and cerebrospinal fluid in parasyphilitic affections contain a marked excess of lipoids, inorganic salts and splitting products of the phosphatides; and that this excess is proportional to the intensity of the disease. I have also found that a cerebrospinal fluid which gives a positive Wassermann reaction, after removal of the protein content by precipitation with alcohol, fails to give the reaction. I am therefore in agreement with Noguchi who, working on the relation of protein, lipoids and salts to the Wassermann reaction, has come to the following conclusions: —

1. The high value in respect to complement-binding exhibited by blood sera from syphilitics and spinal fluids from general paralytics is associated with an excessively high content of globulin, but there does not exist a direct quantitative relation between the two. Cases of secondary syphilis which have been under prolonged and proper medication do not exhibit the globulin increase, and usually fail to give the Wassermann reaction. The active substances entering into the Wassermann reaction are precipitable with the globulin, and chiefly with the euglobulin fraction of the fluids.

2. Temperatures of 70° to 76° C. destroy the active substances. Exposed to sunlight, the active substances deteriorate slowly. A photodynamic substance such as eosin, under the direct influence of the sun, brings about their complete and rapid

destruction. This effect does not occur in the dark. The active substances are subject to tryptic and peptic digestion, and are destroyed by weak acids and alkalies.

3. The active substances in the blood sera and spinal fluids cannot be separated from them or from the globulin precipitate by alcohol.

4. There are contained in the alcoholic extracts of normal and syphilitic blood and organs certain acetone-soluble lipoids which possess high antigenic values for the Wassermann reaction. Cholesterin is inactive, and the bile salts less active than the lipoidal bodies.

5. Sodium cholate is about as active as sodium taurocholate, but neurin and cholin are inactive.

Porges and Meier found that by addition of lecithin certain substances contained in syphilitic serum are rendered evident by a flocculent precipitate, and they have employed this method in place of the deviation of the complement method. But it is generally thought that this precipitation method is not so specific as the Wassermann method; moreover, Neubauer, Porges and Salomon were able to show that syphilitic serum only behaves stronger in this respect than normal serum. Fritz and Kren found that the lecithin test is not absolutely reliable, for non-specific diseases as tuberculosis, lepra, etc., give a precipitation; still less reliable is the test with glycocholate and taurocholate of soda. In respect to the Klausner reaction of globulin precipitation it was found that it was more uncertain than the lecithin and bile salts flocculation.

Neisser, Brück and Stern's investigations are of importance, for they have made a large number of experiments with apes and anthropoid apes, as well as observations on human beings. They conclude that the antigens are not identical with the living virus, nor of the same substance. They do not consider that mercury and atoxyl cause a destruction of the antigen but that treatment by these drugs injures or destroys the spirochaetes. Moreover, it has been found that antibodies exist normally in small quantities in some of the lower apes; it has so far not been found in the higher apes; it is therefore not a new product in syphilis but it is enormously increased in quantity in this disease. They consider that the serum diagnosis researches prove a direct association of syphilis, tabes and general paralysis. Immunity to reinoculation occurs when the virus has become generalised in the blood and lymph (Neisser). It is probable that the generalisation of the virus engenders simultaneously changes in the properties of the serum by which changes it becomes capable of giving the Wassermann reaction and preventing re-inoculation.

There are a number of other reactions which show that a profound bio-chemical change occurs in the blood in constitutional syphilis. Thus Klausner has shown that distilled water added to syphilitic serum causes a precipitation due to the amount of a precipitable globulin which syphilitic

serum contains. Fornet and Schereschewsky have shown that the serum of paralytics and tabetics exclusively give with the serum of syphilitic patients a positive precipitin reaction. It is claimed, therefore, by them that this observation proves the syphilogenous origin of these two diseases.

The simpler method of Noguchi, to which I have been giving attention, consists in boiling two parts of the cerebrospinal fluid with five parts of a 10 per cent. solution of butyric acid in saline solution for a few seconds and then adding one part of normal NaOH solution and again boiling briefly. A flocculent precipitate is obtained in parasyphilitic affections. It is due to the presence of a globulin ; it has before been remarked that there is a parallelism between the presence of albumin in cerebrospinal fluid and the Wassermann reaction.

Summary.—The original method of Wassermann is the most complicated, but is regarded by the majority of investigators as the most specific and reliable. Whatever may be the explanation of the facts all the evidence goes to prove: (1) That these methods in the hands of competent observers afford a valuable means of diagnosis and are especially useful when applied to the cerebrospinal fluid for the determination of the existence or not of general paralysis. (2) That similar substances, whether antibodies or not, occur in the serum of syphilitic and parasyphilitic persons in such quantities as are not found in the serum of normal persons or in the sera of people suffering with other diseases. (3) That similar substances are found in the cerebrospinal fluid of tabetics and general paralytics, and the amount of those substances which cause a deviation of the complement or a precipitation is in proportion to the activity and length of duration of the disease; that these substances are of tissue origin or arise from tissue destruction caused in some way by the action present or past of the syphilitic virus. (4) It is probable that the syphilitic virus excites an increased unloosening of complex lipoid substances containing lecithin and cholesterin, etc., from the red corpuscles and cells of the body. (5) That this prevails through life, and in certain cases of syphilitic infection, viz., general paralysis and tabes, the central nervous system, which under ordinary circumstances is protected against the loss of its lipoid substances, takes part in the process, and this is manifested by the presence of lipoids and globulins in the cerebrospinal fluid, and these act as antibodies in the reaction. This lipoid complex, as well as globulin, increases in amount as the process of neuronic decay proceeds. It is probably owing to the presence of these substances that the granulation of the ventricles, so characteristic a feature of general paralysis, arises as a result of stimulation to proliferative hyperplasia of the ependymal epithelium. Choline may also be present owing to decomposition of

lecithin, but this may occur in any active degenerative process of the myelin, and is not pathognomonic of any particular disease.

Other lipoids of the phosphatide group are present usually in considerable amount and in proportion to the extent of myelin destruction and dissociation. I have pointed this out in the Archives of Neurology, Vol. II., 1902, p. 304, when after referring to the work of Flexner, Noguchi and Kyes on cobra venom I stated that:—

> The products of degeneration of nervous tissues are numerous, and consist not only of choline, but also of a number of bodies of the lecithin group, being various derivations of "protagon." Choline is the most easily separated and recognised physiologically and chemically, and it is possible that the products of degeneration vary according to the cause and nature of the destructive process. Still, there is no evidence to show that these products of degeneration can *per se* produce the clinical manifestations and morphological changes indicating neuronic irritation and destruction of general paralysis, otherwise we ought to get these changes in other diseases, also destructive lesions of the nervous system. Therefore, I think it may be conceived as possible that there is a latent toxin in the blood which combines with endo-complements the products of deranged neuron activity, producing locally (this is, where the neuron metabolism is deranged either by stress, circulatory deficiencies, or hereditary, physiological, or anatomical defects) an active neurolysin proportional to (*a*) the amount of latent toxin in the blood; and (*b*) the amount of endo-complement produced by the deranged neuron metabolism.

Blumenthal states that he has found that the blood of syphilitic persons, also of tabetics and paralytics, contains a large increase of lecithin as compared with the normal. He finds also an increase of lecithin in the fæces in tabes and general paralysis and a great decrease in the bone marrow. He considers that tabes and paralysis are associated with a progressive impoverishment of the body in lecithin. It is more probable that there is an impoverishment of lipoids, including the important substance, cholesterin.

Lecture III.

I endeavoured in my last lectures to indicate some of the advances made in our knowledge of the biology and bio-chemistry of syphilis, and in my final lecture I will try to correlate the facts with clinico-anatomical knowledge, especially in relation to the etiology of the para-syphilitic affections, tabes, and general paralysis.

Parasyphilis (Fournier): Metasyphilis (Moebius).

Parasyphilis is the term given by Fournier to those diseases of which syphilis is essentially the cause, but which are not directly the result of the syphilitic virus. Such diseases are: general paralysis, tabes dorsalis, tabo-paralysis and primary optic atrophy. These diseases

are really a single morbid entity owning the same cause; insidious in onset, progressive in character, and uninfluenced by anti-syphilitic remedies. These various clinical types of parasyphilitic disease are the result of a primary neuronic dystrophy; they have a similar pathogenesis and may occur simultaneously or successively in the same individual. In tabes dorsalis the spinal sensory protoneurons are affected; in general paralysis the cortical association neurons; in tabo-paralysis both are affected simultaneously or successively. The dystrophic process is due to a lack of durability of the neurons; it may be a slow process of decay and death of the intra-spinal portion of the sensory protoneurons, as in the case of tabes dorsalis; it may be a rapid process of decay and death of systems and communities of neurons of the brain, as in general paralysis. The former is a smouldering destruction of neural elements, the latter a conflagration often fanned into flames by microbial toxæmia, autotoxæmia, or circulatory disturbances associated with arterial anæmia and venous congestion with blood stasis of the brain. It is probable that Erb's spinal paralysis and certain cases of amyotrophic lateral sclerosis may be primary post-syphilitic dystrophies.

Fournier thus classifies parasyphilitic affections:—

I. Acquired Syphilis.

1. Acute hystero-neurasthenia of the secondary period.
2. Different neurasthenic manifestations of a more advanced stage.
3. Tabes.
4. General paralysis.
5. A special form of epilepsy.
6. A special form of muscular atrophy.

II. Heredo-syphilis.

Numerous dystrophic troubles, general or partial; malformation, notably dental; arrest or retardation of physical and intellectual development, infantilism, dwarfism, inborn lack of vitality, cachexia, marasmus, rickets, hydrocephalus, certain forms of simple meningitis in early life, possibly certain cases of true epilepsy, juvenile tabes, spinal and optic juvenile general paresis. The gravity of these affections lies in the fact that they are uninfluenced by antisyphilitic treatment. The local and general failure of development may be due (1) to the direct influence of the virus upon the life and growth of the tissues, or (2) indirectly to exhaustion of the specific energy of the cells of the central nervous system by the establishment of an altered metabolism, the bio-chemical

nature of which is not yet fully understood. But, as a provisional hypothesis, we might suggest that the unloosening of lipoid substances into the blood, which we know occurs in congenital syphilis, may lead to a defective *vita propria* of all the cells of the body. In some lesions of congenital syphilis it may be actually due to the local invasions and multiplication of the spirochaete, for they have been found in abundance in situations where local lesions exist, *e.g.*, the epiphysis of bone, and why not in the epiblastic enamel germs.

We might provisionally suggest as a hypothesis that in all cases of acquired and congenital syphilis the living contagium (spirochaete) excites the tissues and fluids of the body to a defensive reaction. The difference in the effects of inoculation may depend upon the virus itself. Some striking examples will be given (p. 38) which apparently indicate that there may be a special neurotoxic virus, and if such instances were more numerous we could hardly believe that coincidence could explain the facts. If, as there is reason to believe, the *Spirochæta Pallida* is the living contagium, and that, becoming generalised in the lymph and blood stream, it produces the secondary manifestations, then there is a certain amount of chance what tissues will be attacked; for the living agent, swept along in the blood stream, may become lodged anywhere, and, by blocking capillaries, cause a local focus of tissue infection. The existence of a generalised eruption implies virulence of the circulating blood, and experiments demonstrate the fact that the blood is virulent during the eruptive stage; thus, Neisser has obtained a positive result by injection of blood into the skin in the chimpanzee, and Roux and Metchnikoff have successfully inoculated a Macaque monkey from the blood of a chimpanzee in the eruptive period. It would be of great interest to know how long the virulence of the blood persists after the generalised eruption, or if the consecutive attacks which may occur even after 15 or 20 years are explained by the "contagium vivum" remaining latent in the lymphatic glands or some deep-seated organ. What is the evidence in favour of this view? It is generally admitted that the subjects of tabes and general paralysis are recruited especially from those individuals who have had a mild attack and who very seldom show any signs or symptoms of tertiary gummatous skin, visceral or bone lesions. Fournier states: "The comparative mildness of the primary constitutional symptoms in those who ultimately become tabetic would almost seem to indicate that, when the syphilitic virus expends itself in severe primary and secondary manifestations, there is a less tendency to the subtle poison which proves so disastrous to the nervous system." From an experience of over 500 *post-mortems* made on paralytic patients, I have been surprised at the rarity of severe tertiary skin and visceral

lesions as compared with the cases of true syphilitic brain disease. Arterio-sclerosis, in the form of fibrotic plaques of the aorta, is, however, very common in paralytic dementia, which, however, is now regarded as a parasyphilitic affection. Again, although paralytics in the prodromal stages of the disease often give themselves up to debauchery and sexual congress with loose women, I have never seen or had my attention called to a case of general paralysis among the vast numbers in the London County Asylums that showed a primary sore or a secondary rash. Krafft-Ebing noted the same fact, and concluded that the reason was that every paralytic had had syphilis and was therefore immune. He caused this hypothesis to be put to a crucial test. Nine cases of general paralysis were selected that gave no history and showed no signs on the body; these patients were inoculated with the virus of a typical hard chancre and watched for 180 days. They presented no signs of infection. The only assumption is that they were immune owing to previous infection, and that they possessed a power of resisting the action of the syphilitic virus. The concordance of this result with the statistical data of antecedent, inherited, or acquired syphilis in cases of tabes and general paralysis given later, led to the widespread acceptance by neurologists of the view that tabes spinalis or cerebralis (general paralysis) is essentially of syphilitic origin. No syphilis, no tabes. Only a few eminent neurologists, such as Von Leyden, refuse to accept the syphilitic origin of tabes, and one of the arguments employed against this view is that anti-syphilitic remedies are of no avail in preventing the disease or arresting its progress. Moreover, we know that many people develop general paralysis or tabes dorsalis, even though they have been treated with mercury systematically from the primary infection onwards. So much has this impressed some authorities that they have even asserted that over-mercurialisation is the cause of the disease in question. The average time which elapses between the primary sore and the onset of tabes and general paralysis is, according to the observations of Schuster, the same in persons who have been thoroughly treated with mercury and those who have either not been treated at all, or only insufficiently. All the facts, therefore, go to prove that the syphilitic virus has in some way or other damaged the durability of the neurones, so that systems or communities die prematurely. It has been observed that Fournier includes other functional and organic diseases of the nervous system among the parasyphilitic affections. We have less knowledge concerning them and their pathogenesis. I have, however, seen cases of general paralysis in which the motor symptoms were most pronounced and the dementia slight, in which all the deep reflexes were exaggerated, and the plantar extensor reflex present on both sides—a very unusual occurrence in the

ordinary paralytic dementia. At the autopsies there was a well-marked sclerosis of the crossed pyramidal tracts without any coarse lesion in the brain and cord to account for it. I have also seen cases of progressive amyotrophic lateral sclerosis occurring in the subjects of syphilis which appeared to be the result of the progressive degeneration of the whole motor efferent tract from cortex to periphery without any sensory disturbance. Some of the cases of Raymond cited by Fournier with sensory troubles, viz., rheumatic pains and paræsthesiae, are obviously, from the account given of the appearances of the spinal cord *post mortem*, cases of sub-acute gummatous meningitis involving the roots. The serum diagnosis and the examination of the cerebrospinal fluid bio-chemically and microscopically will permit us in future to determine whether syphilis is the essential cause of these degenerations. For every nervous disease, whether functional or organic, occurring in a person who has suffered from syphilis is not necessarily syphilitic in origin, yet, when we consider the profound influence the virus has upon the blood and tissues of the whole body, it is not illogical to assume that any disease, local or constitutional, functional or organic, occurring in a person who has acquired or inherited syphilis may possibly have found a suitable soil for development, owing to the diminished vital resistance of the tissues, occasioned by such a potent and persistent poison as syphilis. Thus syphilis, although not a direct agent in such a case, by its devitalising influence and the impoverishment of the lipoids, becomes an important indirect causal factor of the disease in question. There are many known ways in which syphilis can cause functional disturbances of the nervous system and lead to the development of neuroses and psychoses. The theory of the possibility of the syphilitic virus, or the lipoid products of its activity, stimulating the neurons to increased dissimilative action and exhaustion has been shown to have considerable support from recent investigations. (*Vide* p. 28.) There are, however, other conditions which are well known, viz., the change in the blood and blood vessels, and in the lymph and lymph channels. Long ago, Virchow pointed out that in syphilis there is a diminution of red blood corpuscles and a hyperalbuminosis. Later, Schulgowski, Hafter and Laacke described a considerable fall in the red blood corpuscle count. In the secondary stage Martin and Hiller, also Letzius, showed that not only is there a diminution in the number of red blood corpuscles, but also an absolute diminution of the hæmoglobin content of the corpuscle. Anz found, besides the fall in number of the red blood corpuscles, an increase of the white, so that one can speak of a relative and absolute leucocytosis. Later observers showed that there was a diminution of polynuclear leucocytes, and that the

leucocytosis was due to a great increase of lymphocytes, which increase we may associate with the polyadenitis. Further, there is an increase of eosinophils. These changes in the blood in the secondary period increase in intensity with each fresh series of syphilitic manifestations, and diminish as they diminish; moreover, the blood changes disappear with the disappearance of the secondary symptoms under anti-syphilitic treatment. Fournier long ago described the favourable influence of mercury upon the blood formation; clearly, then, the mercury, by its influence upon the productiveness of the syphilitic virus, allows a return of the normal hæmapoietic formation, or arrests a too rapid hæmolytic action. The French authorities were the first to call attention to a syphilitic anæmia, and to point out that iron had no influence thereon. The ebb and flow of the amount of oxyhæmoglobin is correlative to the flow and ebb of lymphocytes, which might indicate that, with the pouring out of an abundance of lymphocytes from the lymph stream into the blood stream, there was associated a pouring out of the virus that occasioned the irritation and hyperplasia of the lymph-cell elements. Hoffmann asserts that he has observed the serum of a syphilitic patient produce immobility and agglutination of the spirochaetes. Perchance it is that when the virus can no longer be neutralised by the defensive reaction of the blood serum embolic capillary effects are produced, causing papular eruptions of the skin, mucous tubercles, and occasionally, meningitis. Selenew demonstrated blood changes before the outbreak of the secondary exanthem, therefore before the secondary incubation stage. It is probable that before the eruption becomes visible, microscopic changes have occurred in the affected cutaneous capillaries and adjacent skin structures, much in the same way as in the primary sore; consequently, we should expect a blood change to precede the eruption. The anæmia may be due to a hæmolysis owing to an unloosening of lipoid substances (lecithins and cholesterin) from the red corpuscles by the action of a toxic substance of the virus acting as a lipolytic ferment disintegrating the osmotic membranes or by chemical interaction in the lecithin and cholesterin complex, forming the osmotic membrane* producing physical changes by which the membrane becomes permeable even to the large hæmoglobin molecules. (Fig. 1.) It may be supposed that the protein stroma of the corpuscle is covered by a film or membrane formed of this lipoid substance, and the virus acts upon it in such a way as to dissolve, dissociate, or destroy the membranous film covering the corpuscle, and causing thereby a liberation of both the hæmoglobin and the

* The idea of the existence of an osmotic membrane was first conceived by Prof. Schafer, as far as I know, in the description of the blood. (Quain's Anatomy, 1893.)

† He gives many facts in support of his arguments in favour of the existence of such a membrane.

lipoid substances into the serum. According to Levaditi and Yamanouchi the lipoids serving for serum diagnosis not only exist in the liver but in other organs, the brain and the red corpuscles. They are probably complexes in which lecithin enters largely. The anæmia may, however, be due to interference with the functions of the hæmapoietic tissues; in support of this is the fact established experimentally by Neisser that the red marrow and spleen are especially rich in the virus. Since mercury can rapidly improve this blood dyscrasia, it is probable that it does so by arresting the development of the *contagium vivum* in these blood-forming tissues. In congenital syphilitic children hæmoglobinuria may occur, and this may be due to the existence of a large quantity of the virus in the blood causing hæmolysis of the corpuscles. Many authorities working at the subject of metabolism in syphilis have shown that the nitrogen metabolism is altered. "Von Boick, Stephanow, and Bjelakow found that the assimilation of nitrogen of food sinks, and the percentage of extractives increases considerably in relation to the urea." (Max Nonne.) This would indicate an altered dissimilative metabolism. There is, therefore, considerable evidence to show that causes exist which render the organs of the body more vulnerable, not only to other infective agencies, *e.g.*, tubercle causing scrofula, but also to the evolution and development of neuroses and degenerations by a devitalising influence on the tissues by the unloosening of lipoid substances. We have now to consider how far do these researches, biological and biochemical, help us in determining the etiology of tabes and general paralysis.

Etiology of Tabes.

(*Tabes Dorsalis, Tabes Optica, Tabo-Paralysis, General Paralysis*)

The Wassermann method of diagnosis has come to strengthen and confirm the belief of many neurologists like myself: "*no syphilis, no tabes*;" this was previously based solely upon statistics and observations relating to the etiology of the disease. Moreover, the etiology and the serum diagnosis are reciprocally supporting not only of the parasyphilitic theory, but also of the view that there is one morbid entity which may be described as tabes; a view first put forward by Fournier, and which I have supported by comparing the clinical notes, and in a large number of instances the *post-mortem* results (with microscopic investigation) of sixty cases of tabes dorsalis and sixty cases of tabo-paralysis. I came to the conclusion that Fournier was justified in asserting the identical relation of the etiology, the close relationship and overlapping in the symptomatology and pathology, and that he was right when he destined them one day or other to be grouped in a single pathological entity; for

Ferrier, in his admirable Lumleian Lectures on tabes dorsalis, says: " . . . and here I would express in concurrence with Fournier, Mott, and many other neuro-pathologists of the present day, my belief in the essential pathological identity of tabes and general paralysis. They are, in my opinion, merely different aspects of the same polymorphic disease." Both are tabetic, or wasting, affections of the sensory proto-neurons in the one case and of the cortical neurons in the other. The essential etiological factor is the same, and the average time elapsing between the primary infection and the onset of the degenerative process corresponds in the two diseases. Fournier remarks that the establishment of the syphilitic origin of tabes dorsalis, from his experience, would necessarily end in the application of the doctrine to general paralysis. In fact, there are so many symptoms in common and so many analogies of evolution and termination associating these two diseases that it was quite natural to conclude the etiology of one from that of the other.

I have endeavoured to show in the Archives of Neurology, Vols. I. and II., and elsewhere, all the evidence of the etiology of tabes and general paralysis tends to prove that there is in all probability one essential cause, syphilis, acquired or congenital, and that there are a number of contributing factors, any one of which by itself or even in combination with others, *e.g.*, sexual excess, mental stress, heredity, injury, alcohol, is not capable of producing the disease. The fact that congenital syphilis leads both to tabes and general paralysis at so early a period of life as to exclude most of the contributory factors except heredity, is an argument in favour of syphilis being the essential cause. Moreover, males and females are affected with juvenile optic tabes, tabes and general paralysis, in equal numbers. Thus, of 500 general paralytics that have died and been examined *post mortem* at Claybury, there were 5 males and 5 females who suffered with juvenile general paralysis; that is, 2 per cent. of the total. I may here remark that this condition was first described by Dr. Clouston. The study of heredo-syphilis in relation to these parasyphilitic affections is especially convincing as to the essential cause of tabes and general paralysis being syphilis. This has been brought home to me in a very convincing manner in the large number of cases in which I have studied the family histories. I will cite a few examples: A young man was admitted to Claybury suffering with what were termed epileptic fits, the seizures did not cease, and he died; externally there was nothing on his body to show that he had congenital syphilis; his liver, however, showed typical signs of congenital syphilis, and the brain was typical of general paralysis. A brother in Caterham Asylum presented the facies of a typical congenital syphilitic. I ascertained that the father died of general paralysis, and the

mother, when I interviewed her, was in the early stage of dementia. I was asked to see recently at Hanwell a young girl who, blind from optic atrophy, had later become demented. I was informed there were no signs of syphilis on the body, and she was one of a large grown-up family. Fortunately the mother was there at the time. I therefore had the opportunity of interrogating her. I found it was quite correct that she was one of a large family, but I also ascertained that, prior to the birth of this child, there had been several miscarriages and still-born children, that this child had suffered with snuffles and a rash, that she had taken it to the hospital, and grey powders had been given. When the rash disappeared, she ceased to attend further. As so often happens in these cases, the mother had not apparently suffered, and showed no signs of syphilis. Another example I may mention: A juvenile paralytic boy was admitted to Bexley and died there; recently his brother has been admitted with commencing signs of the disease. The former had Hutchinson teeth, but no history of syphilis could be obtained from the father. This man died in Guy's Hospital. I wrote to the registrar, and I received the information that he had had syphilis. Perhaps the most convincing case is the following one, which died in Claybury about a year ago: A boy was admitted with dementia, contraction of all four limbs, and epileptic seizures; dying not long after admission, the *post-mortem* examination revealed very advanced general paralysis. There were no signs on the body, and the boy, up to twelve years of age, was bright and intelligent; then mental symptoms set in and steadily progressed. A history from the father showed that five years before marriage he had contracted syphilis, which, in spite of long treatment by an eminent physician, had not been cured, for the first child died within 48 hours of birth, the second within 24 hours, the third suffered with late interstitial keratitis, and later nerve-deafness; then came the patient, and afterwards healthy children. I could multiply these instances, for, altogether, I have notes of some 60 consecutive cases, and in the great majority (over 80 per cent.) there are indubitable signs, or an unquestionable history, as in the above cases, pointing to hereditary syphilis. I have found no case in which I could *certainly* exclude syphilis. Particularly common is optic atrophy, which takes these children to the blind school, and there they develop fits or signs of mental deterioration, and are next sent to the asylum.

The cases of tabes occurring in heredo-syphilis are not nearly so numerous as the cases of general paralysis; the ataxy is usually not very marked, optic atrophy is very common, and tabo-paralysis is met with often associated with optic atrophy; optic atrophy occurs also pretty frequently in the paralytic dementia of congenital syphilis. I have seen

two brothers so affected, and die after developing the signs of progressive dementia. The period of time elapsing between the evolution of tabes and general paralysis and the acquired infection varies considerably; it may be from 3 to 31 years; but the average is 8 to 15 years. The life of the neurons has been reduced, and the time that will elapse between infection and the onset of decay depends upon the intensity of the virus and the inborn resistance of the nervous system, together with other supplemental factors causing stress. In these hereditary cases it is surprising how frequently we find one of the parents, and occasionally both, suffering from paralysis or tabes; this implies an inborn tendency to this degenerative condition. Now it may be asked if twenty-five years, or even more, can elapse in an adult between the acquirement of syphilis and the onset of the symptoms of parasyphilis, why should not the same long period occur occasionally in congenital syphilitic cases, so that instead of the first symptoms commencing at puberty they are not manifest till adolescence, or even considerably later. Nonne relates a case of a workman, aged 32, who had suffered for two years with lightning pains, and had never been infected with syphilis or addicted to drink, and who presented all the typical signs of ataxy. He had been treated in the hospital for severe hereditary syphilis. I have occasionally observed similar cases of general paralysis, *e.g.*: a man aged 28 died recently in one of the London County Asylums of very advanced general paralysis. The disease was first manifested at the age of 18, when he had a fit. His character was strange; he married, had one child born dead, and afterwards his wife left him. He had no signs of syphilis on his body, but I found that his father had died eight years previously in Claybury Asylum. In my Croonian Lectures upon the "Degeneration of the Neuron" I remarked that it is very probable that some of the cases occurring in adults in which syphilis can with certainty be excluded, may still owe the disease to an inherited syphilitic taint. It is not even necessary, as quite one-half of the juvenile cases show, that they should exhibit any external signs of congenital syphilis, for many of the juvenile cases which I collected were proved beyond doubt to be born of syphilitic parents, although manifesting themselves no external signs of syphilis, whereas brothers and sisters exhibited very definite signs. A case of general paralysis died at Banstead Asylum which had previously been under the care of Dr. Percy Smith at Bethlehem Hospital. This woman had characteristic signs of congenital syphilis, but she did not manifest symptoms of progressive dementia till she was 30 years of age. The patient was an unmarried woman, and there was no reason to believe that she had acquired the disease. Recently Christian Muller has put forward the same hypothesis to explain those cases in

which no history of acquired syphilis can be obtained. He describes two cases of women (virgins) who were the subjects of well-marked signs of congenital syphilis, and who died of general paralysis at the ages of 42 and 43 years. The symptoms were not noticeable until a year or two before death.

Dr. Ferrier has in a masterly manner reviewed the evidence which points to syphilis being the essential cause of general paralysis and tabes, and, in conclusion, I cannot do better than quote him:—"One might multiply arguments in favour of the causal relation between syphilis and tabes, but they are unnecessary. For those above related, singly and collectively, leave, in my opinion, little room for doubt that tabes and general paralysis are in all cases of syphilitic origin, and that tabes, *per se*, is as much a proof of antecedent syphilis as a gumma of the skin."

Although syphilis is the essential cause, yet, as Fournier showed, tabes and general paralysis are not syphilitic, but an outcome of syphilis, and the riddle is still unsolved why only about 3 to 5 per cent. of the persons infected with syphilis should subsequently suffer with one of these degenerations of the nervous system termed parasyphilitic. But only 10 to 15 per cent. of persons suffering with diphtheria develop post-diphtheritic paralysis; these are usually cases in which the local infective process was mild and often unnoticed; in that respect, like parasyphilitic affections, which, more often than not, follow mild and even unrecognised primary infection and secondary symptoms. Is it because the virus is attenuated or modified, and, thereby, has acquired a special neurotoxic action, or is it because, in a small percentage of individuals, the cells of the body, *especially the cells of the nervous system*, react to the virus in a hypersensitive manner? As already indicated, there are facts which suggest the possibility of a certain form of virus with a neurotoxic action. Thus, Babinski remarks that it seems possible that a syphilitic virus may sometimes be endowed with a particular aptitude for attacking the nervous system; he reports the case of two students who were infected the same day by the same woman; both died fifteen years later of general paralysis; these students were, however, related. I have recently heard of two professional men, not related, who acquired syphilis about the same time from the same nurse; ten years later they developed general paralysis. Marie and Bernhard relate the instance of two men who were infected from the same source, and ten years later suffered with tabes. Erb narrates an instance of four patients infected by the same woman, who later became the subjects of either tabes or general paralysis, whilst a fifth, who had connection with the woman but was not infected, did not suffer with any disease later. Probably the most striking example supporting this theory of a special neuro-

toxic virus has been afforded by Brosius, who relates that seven glass-blowers suffered with chancre of the lip, and out of five who ten years later came under observation, four suffered with either tabes or general paralysis. If we accept the fact that a spirochaete is the specific causal agent of syphilis, it is conceivable that there may be varieties of this organism, as there are of the malarial parasite or trypanosome. Again, the organism may become attenuated or modified in its passage through the bodies of certain individuals, or it may be attenuated or modified by the action of mercury. It may thus happen that the virus may vary in different cases of infection. This, however, is speculation, and is not supported, but rather contraindicated so far by experiments on animals. For, although lower apes have the disease in a mild form when inoculated from the human being, yet the syphilitic virus of an infected Macacus Rhesus, when used to infect a chimpanzee, appears to have lost none of its original virulence; for the chimpanzee suffers as badly as if it had been infected direct from the human source of the virus. We are probably, therefore, on more certain ground in attributing the variation of the effects which will follow infection, not to the variation of the virus, but to the reaction of the individual himself; and we may represent this in the form of an equation:—

$$\text{Symptom complex } x = \frac{V}{R} = \frac{\text{virus.}}{\text{resistance.}}$$

If the virus V is constant, R resistance must vary. But R is made up of a number of factors, some of which we can ascertain, but it is generally impossible to decompose R into all its constituents. Roughly speaking, we may say that it is made up of what a man is born with, what has happened after birth, and what will happen in the future to resist the reaction of the specific virus, which in the majority of instances is of life-long duration. Most authorities agree that with the widespread syphilisation of a race for many generations, the disease tends to assume a milder form; the effects of the disease are not so severe, and a widespread tendency to an inherited immunity has been brought about. The conversion of a rural into an urban population has done much towards racial syphilisation and to the diffusion of a tendency to inherited immunity, and the begetting thus of a mild form of disease. But, whereas there are fewer cases of severe syphilis than formerly, there are more cases of tabes and general paralysis. The interesting description given by Col. Lamb of the syphilisation of the natives of Uganda shows how severely a race previously free from this disease suffers from malignant skin, bone, and visceral disease. He also points out that tabes is very rarely seen. If we consider some facts concerning congenital syphilis, we must come to the conclusion that immunity is pos-

sible; how, otherwise, can we explain the law of Profeta, viz., the non-syphilitic child of a syphilitic mother does not acquire syphilis from the syphilised mother who suckles it? Again the child may be syphilitic, and the mother shows no signs of syphilis, the mother does not acquire syphilis by suckling that syphilitic child, whereas a wet nurse does. In the former case the fœtus has acquired some antitoxin or something from the maternal blood, which has stimulated its own tissues to react against the virus; in the latter (Colles' Law) the mother has derived from the blood of the syphilised child an antitoxin or something (not the living contagium) which has stimulated her tissues to react against the virus so effectively that she cannot be infected. There is no reason to suppose that the germ cells do not participate in this reaction, seeing that every cell in the body is subjected to the sensitising influence of the chemical products of the virus by means of the blood and lymph. The experiments of Ehrlich have been quoted by Neisser as opposing the view of inherited immunity; on the other hand, Konradi's recent experiments on lyssa support it. The histories I obtained in a large number of cases of juvenile general paralysis and cases of congenital syphilitic nervous disease revealed the fact that the mother very frequently had miscarriages, abortions, and typically syphilitic children, without herself suffering at all, or presenting any signs of syphilis. In two instances the mother died of general paralysis ; in a considerable number of instances the father died of this disease. As a general rule, the result of successive conceptions is as follows: miscarriages, abortions, dead children, children dying in infancy—often of meningitis or hydrocephalus, children who later in life suffer with nervous affections, *e.g.*, nerve deafness, paralytic dementia, optic atrophy, and tabes; and, finally, healthy children. Such a chain of circumstances would undoubtedly indicate that either the virus was becoming attenuated or the resistance to its action was increased. In any case, we have reason to suppose that the children who were born with a syphilitic rash would be immune to reinfection, also those who afterwards suffered with parasyphilis ; Krafft Ebing's observation supports this premise. It is probably a question of the degree of immunity to reinfection that would obtain in the presumably healthy children that followed the diseased ones. But such a chain of events does not always occur, for sometimes children are born with signs of heredo-syphilis after the birth of several healthy children, also parasyphilitic children may be born after the birth of several healthy children. This may be explained by the fact that the specific virus has become active again in the mother, which inference is negatived in most instances by the fact that she herself may say that she has been in good health and no signs of the disease

can be discovered in her. Another explanation offers itself, and it is that the specific virus may have attacked one ovum and spared another. Levaditi has seen the spirochaete within an ovum. No two individuals, even of the same family, are born alike, because the germ-plasm out of which they were formed may be similar, but is not the same; one inherits ancestral tendencies which the other does not; and it may happen, therefore, that a child born later than the healthy children possesses less inborn resistance to the action of the virus; consequently, manifests congenital syphilis or, later, parasyphilis. How can we explain this process of decay of particular groups, systems, and communities of neurons? Why should we have optic atrophy in one individual, atrophy of the spinal portion of the sensory protoneurons in another, decay and atrophy of the cortical neurons in a third, and, in many instances, a decay and atrophy of the whole nervous system? We cannot suppose that it is caused by the random metastasis of the syphilitic organism in the membranes, or coats of the blood vessels, conveyed by the lymph or blood stream, as is probably the case in the true syphilitic lesions of the brain and spinal cord. Everything points against this, for, although parasyphilitic affections present the most varied signs and symptoms, there is one sign usually present which is, for all practical purposes, only met with in parasyphilis, viz., the Argyll-Robertson pupil. No coarse random lesion will explain the constancy of this phenomenon; moreover, this condition, although a sign of syphilitic infection, does not occur in true syphilitic brain disease. Spirochaetes have never been found in the cerebrospinal fluid or antigens. Antibodies are found proportional to the extent of neuronic decay in tabes and general paralysis.

I think all the facts are against the views of Lesser, Bosc, and others that these late manifestations of degeneration of the nervous system may be regarded as quaternary syphilis, a very late effect of the virus comparable with syphilitic orchitis, glossitis, and other sclerous lesions. According to this view, we should be compelled to consider the meningeal and perivascular infiltrations and the glia cell proliferation as the cause of the degeneration. But there are many reasons why we cannot accept this hypothesis. The view I take of the process is that parasyphilitic disease of the nervous system depends upon two factors, intrinsic, innate, and extrinsic, acquired—the soil and the seed; the vital resistance and the specificity of the virus, $\frac{V}{R}$.

All those conditions which may be inherited or acquired, and which tend to active metabolism of systems, communities, and groups of neurons functionally correlated, owing to those conditions of stress causing in one individual spinal neurasthenia, in another cerebral

neurasthenia, will, in conjunction with the effect of the syphilitic poison on the lipoids, cause the nerve-cells to exercise an abnormal metabolic activity.

Ehrlich points out that we cannot suppose that the cells of the body possess, *per se*, an executive defensive capacity to neutralise the noxious effects of all forms of organisms, and his work on hæmolysins shows that the hæmolysin for the corpuscles of a particular animal only occurs after incorporation of the molecules of those corpuscles. But we may suppose that there is an *inherent* aptitude for the cells of the body of certain individuals to adapt themselves readily to defence against the action of the syphilitic virus in a race that has been widely syphilised for generations; consequently, a larger number will have a mild form of the disease. Cases of tabes and general paralysis occasionally arise within three years of the primary sore; possibly this may be due to an inherent hypersensibility to react to the poison. Dr. Byrom Bramwell has recorded a remarkable case of tabes which came on ten months after infection; it would be interesting to investigate the family history and past personal history of these cases to ascertain whether or not it was a second infection.

The nerve-cells are perpetual elements incapable of regeneration, highly differentiated, and complex in structure and function; their centre of nutrition is the nucleus, and when decay sets in, the regressive process attacks first the fine twigs and branches of the tree, the dendrites and dendrons, and the rootlets; in fact, the process is an inversion of its growth and development. But what should cause this premature decay and lack of durability, for the specific energy of the whole of the neurons in the healthy body is sufficient to last until the vital spark dies out? We know the more prolonged duration of infectivity of the syphilitic virus as compared with other contagious diseases, also that one attack of syphilis confers immunity during the rest of the individual's life; moreover, the experiments of Krafft-Ebing are important to remember in this respect. The nerve-elements being perpetual and having acquired a habit of increased metabolic activity, will continue it during life, and will contribute to the excess of lipoids in the blood. When there is no longer metabolic equilibrium, and decay sets in, these lipoid complexes are thrown off in increasing numbers (*vide* p. 25); this seems probable from the fact that in general paralysis and tabes the quantities increase with the progress of the decay. The process of decay will manifest itself in the earliest stages by an increased irritability and functional activity of the nervous structures, often manifesting itself in a *hyperæsthesia sexualis*, emotional exaltation, and, not infrequently, in striking intellectual activity, followed in each case by exhaustion and loss of function. In my second lecture I referred to the fact that the lipoids may be the

products of nuclear activity and the highly *phosphorised* nuclein may be really the source of vital action. We can, therefore, understand how detrimental a hyperæsthesia sexualis is to the vitality of the body.

The uselessness of antisyphilitic remedies is thus easily accounted for; indeed, they are generally positively injurious in true tabes and general paralysis because they lower the vital energy of a system which has over-immunised itself against the syphilitic virus. The only hope of doing any good is by an early diagnosis of the disease and suppression of all those exciting causes which use up the nervous energy and tend to overturn the normal metabolic equilibrium of the nervous structures. Other factors come in determining the location of the degeneration, and although microbial infections and microbial toxæmias are not directly responsible for these parasyphilitic affections, yet they may be an exciting agent in the onset of the disease, to the aggravation of the symptoms, to the acceleration of the progress of neural decay and the fatal termination.

I have often observed when influenza, dysentery, or pneumonia were prevalent in the asylums a number of general paralytics died after a succession of epileptiform or apoplectiform seizures, and I have found, *post mortem*, that they were suffering from one of these morbid infections. It is a common thing to find on the *post-mortem* table patches of broncho-pneumonia and recent active tuberculosis, the appearances of which would accord with clinical notes in the case-book reporting the occurrence of seizures ; and, if the brain be examined microscopically, it is quite easy to prove that these fits correspond with acute degenerative changes, doubtless caused partially by congestive stasis and partially by a toxic condition of the blood exciting and accelerating the process of neural decay. Bacterial invasion, *secondary or terminal*, of the organs of the body of a *non-specific* nature, therefore, may accelerate the morbid process of decay or bring about a fatal termination.

In conclusion I wish to express my obligations to the President and Fellows of the College for their kind attention, as I am not unmindful of the distinguished lecturers who have preceded me; I feel that I have dealt imperfectly with a very difficult subject still in its infancy, but of the greatest importance to medical science and practice, and I can only hope that the words of the old philosopher, Lucretius, may come true, "that one thing after another will grow clear, and dark night will not rob you of the road, to keep you from surveying the utmost things of nature ; in such wise things will light the torch for other things."

BIBLIOGRAPHY.

Lecture I.

Metchnikoff. Microbiology, vol. 1, System of Syphilis, Oxford University Press.

Hoffmann. Die Œtiologie der Syphilis, Berlin, 1906.

Neisser. Die Experimentelle Syphilisforschung, Berlin, 1906.

Levaditi et Yamanouchi. L'orientation de la Syphilis, Compt. rend. de la Société de Biologie, 1908, vol. lxiv.

Ibid. Annales de l'Institut Pasteur, Tome xxii., Nr. 10, Oct. /08.

Bertarelli. Transmission de la Syphilis à la cornée du lapin, *Rivista d'Igiene*, 1906, vol. xvii. et xviii.

Gautier et Maloizel. *Revue de Neurologie*. Sept., /07, p. 959.

Boidin, L., et Weil. Méningite Syphilitique secondaire aiguë, *Presse Médicale*, No. 85, p. 681, Oct. 19/07.

Spielmeyer. Die Trypanosomenkrankheiten, Fischer, Juni /08.

Castellani. *Deutsche Med. Wochenschrift*, 1905, Nr. 43, 1712.

Lingard. Report on Dourine. Calcutta Government Printing Office, India.

Rosenheim. The Bio-chemistry of Animals and Plants. A comparative study. *Science Progress*, Nos. 8 and 9, April and July /08.

Munk. Über lipoide Degeneration. *Virchow's Archiv*. Bd. 194, p. 527.

Levaditi et Yamanouchi. *Ibid.*

Lecture II.

Wassermann. Ueber die Entwickelung der Sero-diagnostik gegenüber Syphilis, II. Mitt., *Berl. Klin. Wochenschrift*, 1907, Nrs. 50 und 51.

Citron. Ueber Komplements-Bindungsversuche, &c., *Deutsche Med. Wochenschrift*, 1907, Nr. 29.

Plaut, F. Sero-diagnostik der Syphilis Zentralblatt f. Nervenheilkunde und Psychiatrie. Heft. 8, 1908.

Meier, G. Die Technik, Zuverlässigkeit und Klinische Bedeutung der Wassermannschen Reaktion auf Syphilis. *Berlin Klinische Wochenschrift*, 1907, Nr. 57.

Levaditi et Yamanouchi. Le Séro-diagnostik de la Syphilis. Société de Biol., Comptes-rendus, T. lxxii., No. 35, p. 240.

Idem. Séro-réaction de la Syphilis et de la Paralysie générale, *idem*, T. lxiv., No. 1, /08.

Idem. T. lxiv., No. 8, p. 349.

Idem. La réaction de la déviation du complément dans la maladie du sommeil. Bulletin de la Soc. de Pathol. exotique, Tome I., No. 1.

Sachs & Rondoni. Beiträge zur Theorie und Praxis der Wassermanschen Syphilis Reaktion. Zeitschrift für Immunitätsforschung und Experimentelle Therapie. Dec. 21/08.

Brück, C., & Stern, M. Die Wassermannsche. A. Neisser. Brücksche Reaktion bei Syphilis. *Deutsche Med. Wochenschrift*, 1908, Nrs. 10—12.

Fornet & Schereshewsky. Sero-diagnostik bei Lues, Tabes, und Paralyse durch specifische Niederschläge, *Münchener Med. Wochenschrift*, 1907, Nr. 30.

KLAUSNER, E. Ueber eine Methode der Serum-diagnostik bei Lues. *Wien. Klin. Wochenschrift*, 1908, Nr. 11.

FRITZ & KREN. Ueber den Wert der Serum-reaktion bei Syphilis nach Porges. Meier und Klausner. *Wien. Klin. Wochenschrift*, 1908, Nr. 12.

NOGUCHI. The Relation of Protein, Lipoids and Salts to the Wassermann Reaction. *The Journal of Experimental Medicine*, vol. xi., No. 1, 1909.

LECTURE III.

BLUMENTHAL. *Neurol. Centralblatt*, 1908, p. 1006.

FOURNIER. Les affections Parasyphilitiques.

MAX NONNE. Syphilis des Nerven-systems.

HOFFMANN. *Ibid.*

NEISSER. *Ibid.*

ROUX & METCHNIKOFF. Metchnikoff *ibid.*

KRAFFT-EBING. Discussion upon General Paralysis. Internat. Congress, Moscow. Ref. *Neurol. Centralblatt*, 1897.

SCHUSTER. Hat die Hg. Behandlung der Syphilis Einfluss auf das Zustandekommen Metasyphilitischer Nervenkrankheiten. *Deutsche Med. Wochenschrift*, Dec. 12/07.

VIRCHOW. Ueber die Natur constitutionell Syphilitischer Affectionen. *Virchow's Archiv. für Path. Anal.*, Bd. xv., 1858.

SCHULGOWSKY. Blutuntersuchungen mittelst des Hæmatometers von Hayem. *St. Petersburg Med. Wochenschrift*, 1878.

LAACHE. Die Anæmie, 1883.

MARTIN & HILLIER. Ref. Max Nonne, *ibid.*

LETZIUS. Max Nonne, *ibid.*

MOTT. *Archives of Neurology*, vols. i., ii., iii.

Croonian Lectures "The Degeneration of the Neuron," *Lancet*, 1900.

FERRIER. Tabes Dorsalis. The Lumleian Lectures, 1906.

MÜLLER, CHRISTIAN. *Münchener Med. Wochenschrift.* Sept. /08.

LAMB, COL. Article: Syphilis in Uganda. *Lancet*, /08.

KONRADI. Ist die erworbene Immunität vererbar? *Centralblatt für Bakt.* Bd. xlvi., Nrs. 1 und 2.

KRAFFT-EBING. *Ibid.*

LESSER. Zur Etiologie und Pathologie des Tabes, speciell ihr Verhältnis zur Syphilis, *Berlin Klin. Wochenschrift*, /04, Nr. 4.

BOSC. Les Maladies bryocytiques. *Centralblatt f. Bakt.* Abtrüg, Bd. xlii., Heft. 5.

LESSER. Ref. Bosc.

EHRLICH. Croonian Lectures. Proceedings of the Royal Society, /04.

BRAMWELL. An analysis of 263 cases of Tabes. *British Medical Journal*, /08.

Ibid. *Lancet*, Nov. 14/08. Report of Meeting of Edinburgh. Medico-Chir. Society.

A CASE OF GUMMATOUS MENINGITIS IN A CONGENITAL SYPHILITIC.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

E. M. A. Female, aged 16 years. Admitted to Claybury Asylum 30/8/05, died 8/7/06. Previously a maid servant, and had done general work for her father for the last two or three years.

History obtained from patient's father.—Father, interviewed by me, gave the following history. His occupation had always been that of a coachman. No insanity on his or the mother's side. The mother of the deceased girl died when the girl was six months old. He married at the age of 20, his wife being a single woman before marriage, and a servant. I could obtain no history of venereal disease or excessive indulgence in alcohol. There were five children born alive, and three miscarriages. The first three pregnancies resulted in miscarriages, and then followed five children born alive, of whom the deceased girl was the last to be born. The rest of the children were all healthy and alive, with the exception of one little boy, who died at the age of nine years. I could obtain no information regarding the cause of the mother's death, except that she had dropsy.

The deceased girl was always delicate from birth. She had snuffles and convulsions, and was treated with grey powder. No history of rash. She was intelligent, quiet, and always reading, and nothing unusual was noticed until 18 months ago, when she became much quieter and forgetful, and would say funny things to her step-mother, and laugh if rebuked. About one year ago she suddenly left her father for no apparent reason, and went to her sister, with whom she stayed. Here she started singing and dancing, and became excitable; a doctor was sent for, she was removed to the infirmary, and thence to Claybury Asylum. The deceased girl never had any fits and was not of a worrying disposition. She fed and lived well. She was intelligent at school, and passed the sixth standard. The father married a second time, but at the present time there have been no children or miscarriages.

The patient, on admission to the Asylum, was considered to be suffering from congenital imbecility and mania. The case book notes state that she was excited, garrulous, and incoherent, singing snatches of comic songs and hymns. She appeared to be weak-minded, but her ability to

remember songs and their words was wonderful. It was observed that she was undersized, poorly nourished, and had Hutchinson teeth. (*Vide* Fig. III.) The knee-jerks were present, and there was slight internal strabismus of the right eye. The official notes from this time onwards are of no interest till the day before her death, when she is said to have had a seizure of the right side of her body and the left side of her face, followed by coma with stertorous breathing. There was an internal squint of the right eye. I obtained the following further information from the nurse: she was childish in her voice, speech, and actions, and amused herself with dolls and picture books, and made no attempt to read or write. (There must, therefore, have been considerable dementia, for I ascertained from the father that she had passed the sixth standard at school). She was faulty in her habits, but was afterwards sorry when corrected.

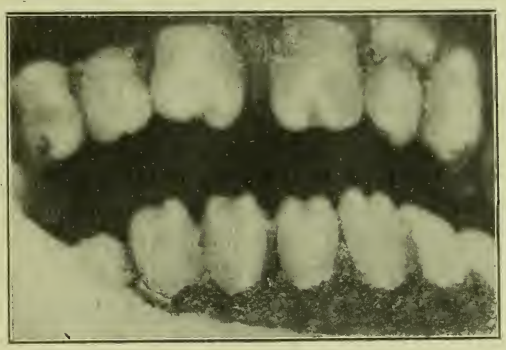


Fig. III

Teeth of the patient. Photograph taken after death.

She was amiable, obedient, and affectionate, and a favourite with the nurses and patients. She had no delusions or hallucinations, and until the day before her death never had a fit. She would occasionally make mistakes as regards personal identification, and would call the nurse, mother. She never menstruated while in the Asylum. She took her food and enjoyed it. The songs she sang and her conversation did not lead the nurses to suppose that she had been immoral.

For three months before she died, she had stiffness and rigidity of the neck, holding her hand in such a manner that the doctor examined her several times for caries of the spine. She had then become helpless and drowsy, taking nourishment badly, and no longer singing her comic songs.

Summary of autopsy.—The brain weighed 1,125 grammes. It was soft and œdematous. There was excess of subdural fluid and the convolu-

tions were flattened. The convolutional pattern was good, and of average complexity; the Sylvian angle was also good. The whole of the base of the brain was covered with a greyish yellow deposit or membrane in places semi-fluid, but otherwise of fairly firm consistency and tough. On stripping this off, the brain substance beneath was left pitted, a similar condition was found on the orbital surface of the frontal lobes, and the mesial aspect whereby these were adherent. A greenish-yellow gelatinous semi-fluid material covered the anterior perforated spots and spread up the Sylvian fissures on both sides. On the under surface of the cerebellum there was a small maroon-coloured swelling. The vessels at the base of the brain and their extensions into the fissure were much thickened, and had a dirty greyish-yellow appearance, like dirty wash-leather. In places the lumen of the arteries of the circle of Willis was either partially or completely obliterated (*vide* Fig. 3, Plate IV.). The middle ear and nose were carefully examined to see if there was any cause for this meningitis, but without success. Cultures were made, and no pyogenic organisms were found. The ependyma of the fourth ventricle showed marked granulations.

The same deposit observed at the base of the brain was found extending down the spinal cord lying in the subarachnoid space. This greyish-yellow gelatinous exudation, after hardening in formalin, formed a firm tissue, which was especially thick in the region of the cervical enlargement, being there 3 or 4 mm. in thickness. The vessels and large arteries of the central nervous system appeared like solid cords or threads of varying thickness, they did not collapse on pressure. When cut through, the sections showed markedly thickened walls, and the lumen in some instances was obliterated.

The liver was denser than natural, otherwise there was no naked-eye change. The aorta showed slight atheroma. There was no evidence of tubercle, the lungs only exhibited bronchitis, congestion, and œdema.

Sections of the cortex cerebri, cerebellum, pons, medulla, optic nerve, arteries of the circle of Willis, and the spinal cord at various levels were made and stained by hæmatoxylin and eosin, and polychrome methylene blue and eosin.

Histological Changes.

Cortex cerebri.—The meninges were infiltrated with lymphocytes and plasma cells, the pial vessels were markedly affected and the lumen diminished by this infiltration; in places where the meningitis was most marked, the infiltration was extending along the pial sheaths into the substance of the brain; but, as a rule, there was little or no change in the vessels in the cortical substance. The perivascular infiltration, then,

was clearly an extension from the meninges. There was little or no subpial felting or glia proliferation, and the columns of Meynert were not distorted in sections of the middle of the first frontal convolution. In the ascending frontal, however, there was much more evidence of affection of the vessels of the cortical grey matter; in fact, there was a very definite patchy encephalitis, and a very definite and abundant formative proliferation of the connective tissue cell elements of the small vessels and pial sheaths, so as to diminish or completely obliterate the lumen of the vessel. It seems that the process was an extension from the meninges, for it was much more marked on the superficial vessels.

In a section stained by hæmotoxylin and eosin of such a vessel examined with an oil immersion lens, the perivascular sheath—and even the lumen of the vessel—was filled with branching connective tissue-cells, the body and processes of which stained pink; lying in these pink-stained cells were purple, round, oval, and irregular nuclei in little clusters, the result of rapid division. The appearance was exactly the same as those observed in chronic trypanosome affections. The neuroglia cells appeared to be undergoing an active proliferation in the superficial layers of the cortex. In the cortical exudation and infiltration there were numerous plasma cells, and in places the neoplastic cell formation was undergoing a granulo-aqueous degeneration; plasmolysis and nucleolysis were very evident. Here could be seen the cells taking the eosin stain diffusely; they had a fainter and less brilliant staining reaction, and large numbers could be seen containing granules of chromatin of varying size. No micro-organisms were seen. The vascular changes indicating subacute meningo-encephalitis were very suggestive of acute general paresis.

The cerebellum showed the same periarteritis and endarteritis, and in the place where there was a maroon-coloured swelling, microscopic examination showed a hæmorrhage of some standing. All the vessels in the neighbourhood were profoundly affected in the manner described above and figured, Plate II., Figs. 4 and 5. The meningeal and perivascular and vascular neoplastic formation extended all the way down the spinal cord; it is shown in the accompanying photomicrographs, Figs. 1 and 2, Plate IV. No tubercle bacilli were discovered by appropriate methods of staining, no pyogenic organisms were obtained by culture, and no organisms were observed in the sections stained by polychrome-eosin to account for this meningo-encephalitis and meningo-myelitis. The infiltration around the optic chiasma was especially marked. It is difficult to understand why the child's sight was not more seriously affected, seeing that the perivascular infiltration had extended some distance into the chiasma. Very probably it was, but the child in the later days of its illness was in a too demented and stupid

state for it to be discovered. Curiously enough, although the child had a stiff neck and a squint, apparently no attempt was made to examine the fundus.

All the arteries of the circle of Willis showed profound periarteritis and obliterative endarteritis (*vide* Fig. 3, Plate IV.). The meningeal and perivascular neoplastic infiltration was universal; it corresponded entirely in its histological character with a gummatous meningo-encephalitis. Polymorpho-nuclears were conspicuous by their absence ; the neoplastic formation consist of proliferated, branched, and spindle-shaped connective tissue-cells, and round or oval cells in which there was a distinct cytoplasm of varying thickness forming all grades between lymphocytes and plasma cells ; there are also large macrophages. Large numbers of the cells were undergoing a granulo-aqueous degeneration, but the course of the disease was too intense and short to allow of absorption of the products of nucleolysis and plasmolysis and leave the connective tissue-cells to go on to the formation of fibrous tissue. Exactly the same sections of the cortex stained to display fibres showed some degeneration and destruction of the tangential system, but there was no marked evidence of sub-pial glia proliferation, nor was there any sub-pial felting ; the perivascular infiltration clearly was an extension from the pia-arachnoid along the pial sheaths. Considering the universal vascular change and perivascular infiltration, it was astonishing how little destruction of cells and fibres had occurred. This can be correlated with the fact that there was comparatively little naked-eye wasting of the cortex. The cells in the superficial layers of the cortex are undoubtedly more affected than the deeper layers, and this is most marked in those patches of cortex where the chronic inflammatory process has extended most along the pial sheaths.

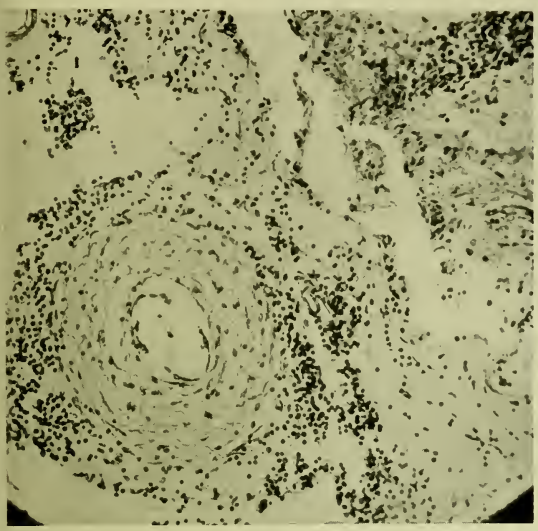


FIG. 1.

Section of lumbo-sacral spinal cord showing chronic gummatous leptomeningitis extending along the small vessels into the substance of the spinal cord. Mag. 200.

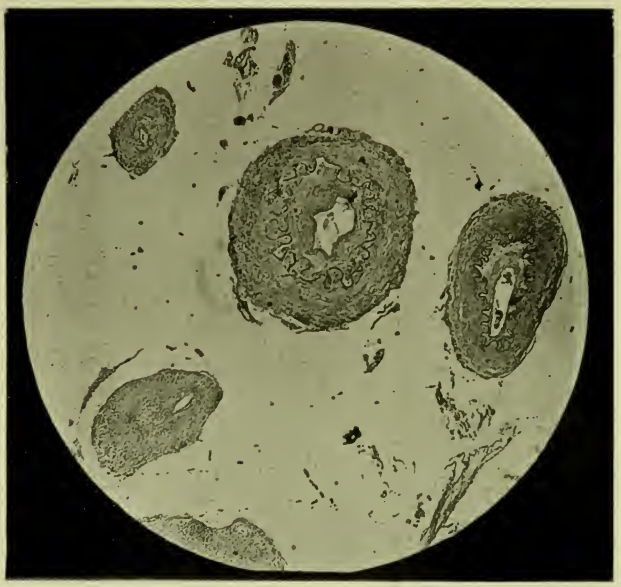


FIG. 3.

Section of various basal arteries showing obliterative arteritis. Mag. 15.

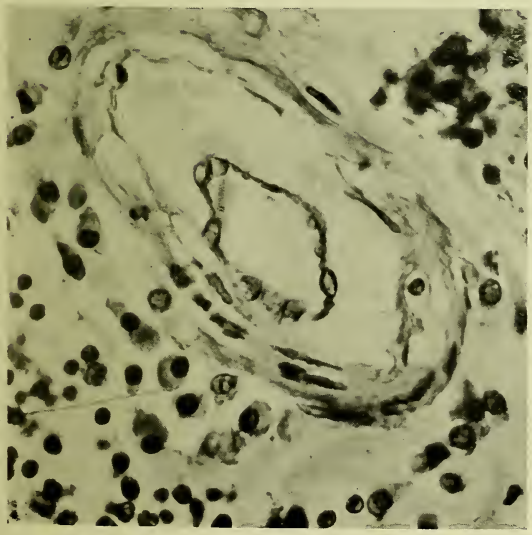


FIG. 2.

Section of the membranes showing the character of the formative cell hyperplasia, *l.* lymphocytes, *p.* plasma cells. Mag. 700.

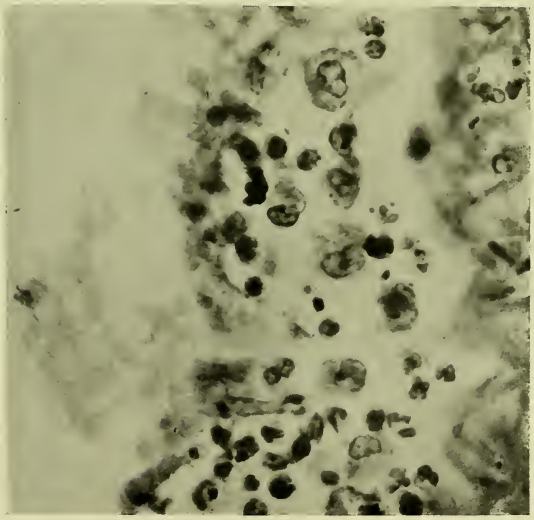


FIG. 4.

Section of the endarterium, showing lymphocytes and plasma cells undergoing granular degeneration. Mag. 700.

A CASE OF LOCALIZED SYPHILITIC PACHYMENINGITIS CEREBRI WITH SPEECH AFFECTION.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

A. G. Aged 44 years. Admitted to Hanwell 13/3/08 for epilepsy, loss of memory, and aphasia, from which she for a time improved. The history obtained showed that her husband had had syphilis eight years ago. She had been married over six years to him. She was his second wife, and has had no children or miscarriages by him. There were several papery scars on the body, and there was some slight glandular enlargement, but the signs of syphilis were not distinctive. Still, the symptoms pointed strongly to syphilis, and in my judgment it was desirable at once to push anti-syphilitic treatment with mercurial inunction after attending to a bad condition of pyorrhœa alveolaris and stomatitis.

I saw this patient on 17/5/08, my attention being called to the case by Dr. Daniel, under whose care she was. I found paresis of the right lower half of the face, with marked deviation of the tongue to the right. She was unable to close the right eye independently of the left, although she could wink and close the left eye independently perfectly well when asked to do so. There was some weakness of the right hand as compared with the left, and the deep reflexes were increased. She tried to talk, but her speech was hardly intelligible, although she understood all that was said to her, as was shown by her obedience to all commands and the endeavours she made to reply to questions; it appeared that her condition of speech defect might be due to dysarthria rather than aphasia, for her utterances were intended apparently to represent her silent thoughts. She is unable to read or write, and, therefore, could not be tested in this respect. I saw her in several fits. The fits come on quite suddenly; when asked whether she knows when a fit is coming on, she points to her tongue and lower half of the right side of the face. I asked her if she felt a numbness there, she responded in the affirmative. She does not lose consciousness, as she will obey commands while the fit is proceeding. The fit starts in a spasm of the muscles of the lower part of the right side of the face and jaw, this spreads up and down to the right orbicularis palpebrarum and corrugator supercilii, which are thrown into spasm, also the platysma of the neck. I thought there was some deviation of the eyes

to the right on one occasion, but she was able to look to the left when told to do so while the fit was proceeding. The spasm of the orbicularis palpebrarum spread to the opposite left eye and the eyeballs rolled upwards; it did not spread to the opposite lower face, nor did it spread to the arm. She has never complained of headache, but there was a tender spot on pressure just above the attachment of the left ear to the skull. There was no optic neuritis and no vomiting. The diagnosis I made was gummatous pachymeningitis over the region of the left ascending frontal and parietal convolutions at their lower extremity, involving especially the tongue area, also probably the pars basilaris of the third frontal.

Subsequent Notes by Dr. Daniel.

May 17th, 1908.—The notes state that the fits continue on an average about 50 a day. One fit lasted about 30 minutes (probably it was a series fused together), but it is interesting to observe *that she remained for* $1\frac{1}{2}$ *hours unable to speak at all.*

May 20th, 1908.—She has had 50 fits in the night, and they are occurring every few minutes in the morning. Yesterday she complained of numbness and pains down the right arm. To-day *there is distinct deviation of the eyes to the right during the tonic stage of the convulsion,* and the fits are occasionally attended by loss of consciousness. She is now being treated by mercurial inunction twice a day.

May 26th.—The notes state that the fits now extend to the right arm, and various sedatives were given, including hyoscyin 1-50th grain, which, it is stated, has had a marked effect; she has had fewer fits and is markedly drowsy this morning; the pulse is feeble and rapid.

May 30th.—A difficulty in swallowing has been observed, and there seems to be an actual paresis. Fits continue practically uncontrollable.

June 1st.—The fits ceased, but patient died June 2nd at 4.35 p.m.

On June 3rd I made the *post-mortem* examination.

On removal of the calvarium, a pachymeningitis about the size of a florin was observed in the region of the tender spot noticed during life just three-quarters of an inch above the attachment of the left ear. On opening the dura mater the thickening was very definite. It was about five times as thick as the normal dura mater. This thickening was uniform, except at the circumference, where it gradually sloped off. It was red and inflamed both externally, in contact with the bone, and internally, in contact with the pia arachnoid. The bone in contact with the inflamed dura was roughened, and there was a slight degree of osteitis; the middle meningeal artery passed through the middle of the patch. Internally the pia arachnoid was red and inflamed, but there was no symphysis with the dura mater in this situation. One inch and a quarter

further back the dura mater was a little thickened (twice the normal) and adherent to the pia arachnoid, so that on stripping, erosion of the surface of the brain occurred over an area the size of a florin at the end of the fissure of Sylvius, involving the posterior end of the first temporal, the adjacent marginal, and, to a very slight extent, the angular gyrus.

Upon close examination the anterior patch of pachymeningitis showed several small caseous nodules about the size of a hempseed; it was found to be situated exactly over the lower end of the ascending frontal and the adjacent inferior frontal and ascending parietal convolutions. There can be no doubt that this gummatous pachymeningitis was the cause of the Jacksonian epilepsy; and it could have been removed by operation with the greatest of ease. At the autopsy no organic disease of other organs, nor of the brain itself, was found; and it was a great pity that the patient was not sent to a hospital as I recommended, for, in my judgment, it was a most suitable case for surgical treatment. She would have been transferred at once had there not been legal difficulties and formalities to overcome.

Microscopical Examination.

I. Portions of the following structures were hardened in formalin and cut after being embedded in paraffin:—

(*a*) The syphilitic pachymeningitis, the cortex beneath comprising pars basilaris, ascending frontal and ascending parietal convolutions. A portion of the corresponding cortex of the right hemisphere was taken for comparison.

(*b*) Portion of the posterior part of the left first temporal and adjacent marginal convolution.

(*c*) The medulla oblongata at the level of the olivary bodies.

(*d*) The cervical enlargement of the spinal cord.

The sections 10μ in thickness were stained by Nissl, polychrome, Giemsa, Van Gieson, and Heidenhain eosin methods.

II. Portions of the tissues (*a*) and (*b*) were taken after the brain had been in formalin for 24 hours and prepared by the Cajal method.

Description of Histological Changes.

The pachymeningitis.—The fibrous bundles of the dura were swollen and separated by an infiltration of lymphocytes and plasma cells; these were unequally distributed, in places forming little nodular aggregations. Moreover, in some situations these collections of cells had undergone necrobiosis and transformation into a granular mass of detritus quite typical of a gumma. The sections showed the middle meningeal artery in transection, also some of its branches; the latter showed a

marked periarteritis, that is the adventia, was infiltrated with young cells; but the main trunk not only showed this condition, but also almost complete obliteration of the lumen by endarteritis. (*Vide* Fig. 4.)

The cortex beneath the pachymeningitis.—The pia arachnoid showed very little cell infiltration, and there was next to no extension along the pial sheaths of the vessels, and this accorded with the fact that there was no symphysis of the dura to the soft membranes. The superficial layers of the cortex exhibited a marked proliferative hyperplasia of the neuroglia cells (*vide* Fig. 5), especially evident in sections stained by all the methods mentioned when a comparison was made with the corre-

FIG. 4.
Photomicrograph of the middle meningeal in gummatous pachymeningitis
Magnification 85.

sponding cortex of the right side. (*Vide* Figs. 1 and 2, Plate V.) I do not think this glia proliferation could be accounted for by the wasting of the neural elements, but it was a direct expression of irritation caused by the superjacent inflammatory condition of the dura (possibly toxic chemical substances). There was some degree of atrophy of the tangential fibres, otherwise the fibre systems appeared as intact in this region of the left hemisphere as in the same region of the corresponding hemisphere. The columns of Meynert of the pyramidal layer were intact, the apical processes of the cells were straight, and

exhibited no cork-screw appearances; but it was possible that their ultimate termination, as well as the terminations of the Betz cells in the tangential layer were damaged or destroyed; otherwise the outline of the cells corresponded with the outlines of normal cells. By Nissl staining the cells showed large clear nuclei and a marked deficiency of chromophyllous substance. The tigroid substance was almost absent in the body of the cells and on the dendrons in sections of the left ascending frontal. A similar appearance was observed in the right ascending frontal, but it was not nearly so intense; there was more chromophyllous

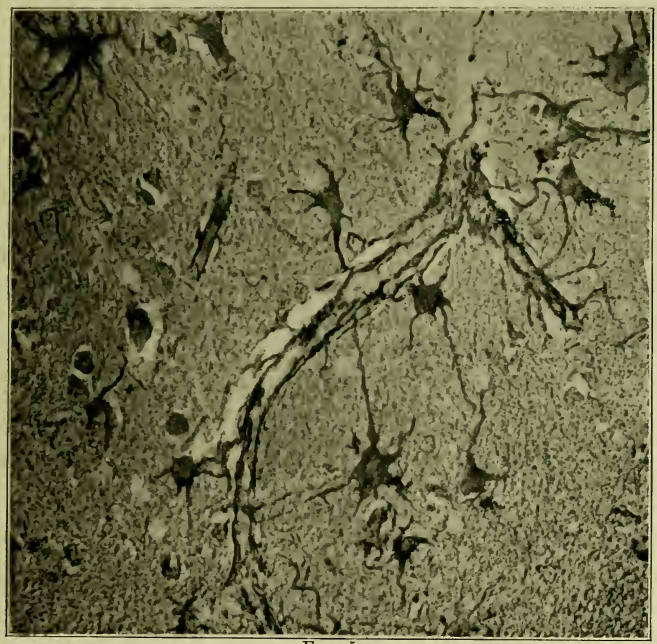


FIG. 5.

Photomicrograph of cortex of left facio-lingual area stained by Cajal fibril method; it shows remarkably well the neuroglia cell hyperplasia and their extensions on to the walls of the small vessels. Magnification 330.

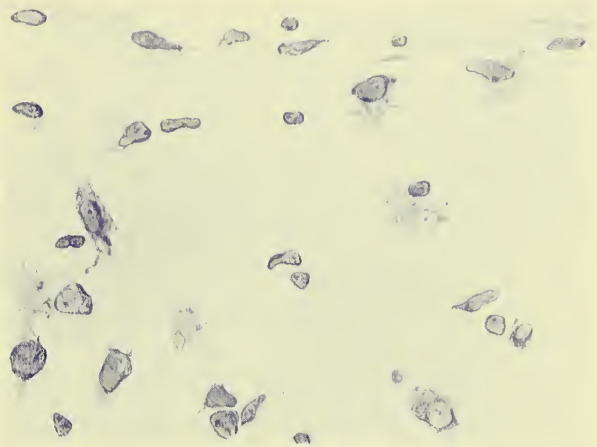
substance, and the cells stained less faintly. (*Vide* Figs. 1 and 2, Plate V.) By the silver method, fibrils could be seen running through the cells, and there was apparently not very much change.

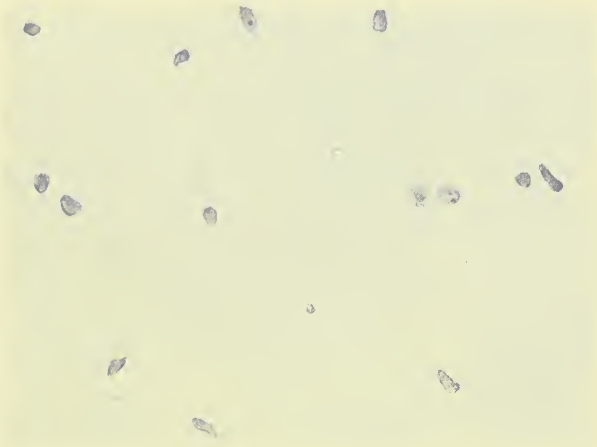
The sections of the cortex at the end of the left Sylvian fissure exhibited very similar changes, but owing to the adhesion of the pia arachnoid to the dura, the cortex presented an eroded appearance; apparently the inflammatory process in this lesion started in the pia arachnoid instead of *within* the dura; it was more recent in origin and less extensive. There was a marked glia proliferation, and the same changes in the layers of cells noted in the other lesion.

Medulla oblongata.—Examination of the medulla oblongata showed a

marked diminution, and, in some cases, absence of chromatic substance in the cells of the facial, hypoglossal, and spinal accessory nuclei on both sides. It was thought that the right nuclei were more affected than the left, but it is difficult to be in any way positive about this. There could be no question that, compared with the appearance of the Nissl pattern of the cells in the anterior horns of the cervical enlargement, both the Betz cells of the motor cortex and the cells of the above-mentioned motor nuclei of the medulla oblongata showed a marked diminution of the chromatic substance; although some of the cells of the anterior horns of the spinal cord were not quite up to normal standard. From these facts it may be inferred that the cells where the primary lesion was acting as a cause of excitatory discharge, giving rise to Jacksonian epilepsy, exhibited the most notable signs of exhaustion, as measured by diminution or absence of chromatic substance. This could not be due to *post-mortem* change, because the cells of the anterior horns of the spinal cord showed a fairly normal Nissl pattern; nor, for the same reason, could the changes be due to the administration of drugs to control the fits prior to death, and it is permissible to assume that the most marked absence of Nissl granules observed in the cortex situated beneath the primary dural lesion may be explained as a result of exhaustion from discharge of energy in the local epileptiform fits produced by the local irritation. Subsequently the fits spread and became generalised, consequently the cells of the cortex of the right hemisphere showed some degree of exhaustion.

Association of the symptoms presented during life, with the lesions observed post mortem.—Undoubtedly the dysarthria and the Jacksonian epilepsy which I observed were in the main due to the pachymeningitis involving the lower end of the Rolandic fissure; but was the conjugate deviation (at that time hardly observable and certainly of later manifestation than the facio-lingual epilepsy) due to this lesion, or to the leptomeningitis involving the cortex behind the posterior end of the Sylvian fissure? The conjugate deviation to the right was only beginning to be manifested on May 17th, but later it became quite definite. In point of time of its initial manifestation it would coincide with the development of this lesion, although it might be explained by an extension of the zone of irritation caused by the anterior lesion, for clinical observation showed that the facio-lingual spasm was followed by tonic and clonic spasm of the right arm, at the time the conjugate deviation of the eyes to the right was noticed. It has been shown by Wilson that there is an association of pricking of ears and conjugate deviation of eyes. Moreover, cases have been recorded of conjugate deviation of eyes resulting from lesions in this temporal region.





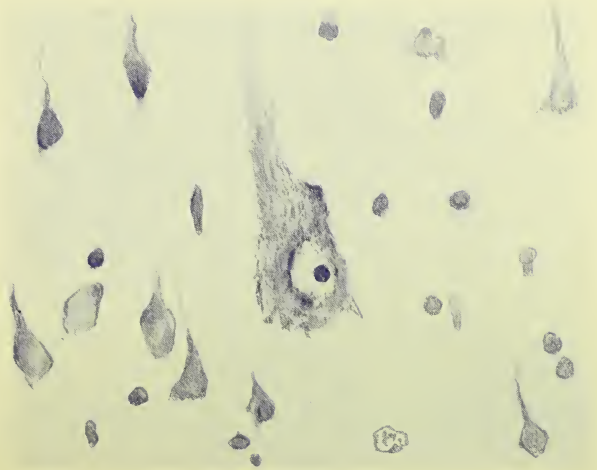


FIG. 1.

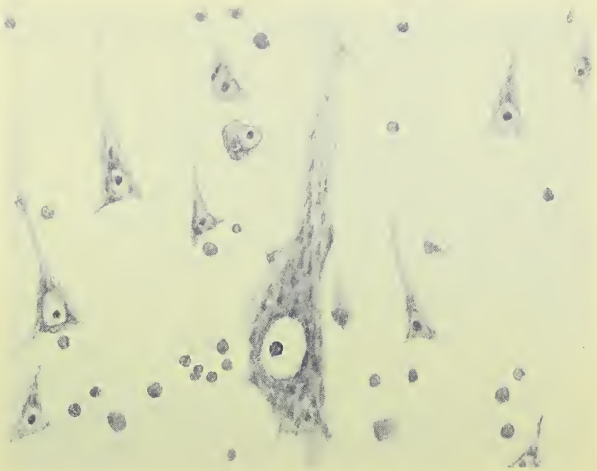


FIG. 2.

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DESCRIPTION OF PLATE V.

FIG. 1.—Camera lucida drawing of small portion of left facio-lingual cortex beneath the pachymeningitis. The superficial molecular layer is shown and the fourth layer; the intervening pyramidal layers are not shown. It will be observed that in comparison with a similar portion of the cortex of the right hemisphere there is a marked hyperplasia of the neuroglia cells. These cells are undergoing active proliferation, the cytoplasm is markedly increased. There is a large Betz cell seen in which the Nissl granules are only very faintly seen, although the outline of the cell is not materially altered.

FIG. 2.—Camera lucida drawing of small portion of the right facio-lingual cortex. The glia cells are smaller, less numerous, and show but little hyperplasia as compared with those seen in Fig. II. A large Betz cell is shown; this exhibits a normal appearance, except perhaps the Nissl granules are not quite so large and distinct as in a normal brain.

Both Figs. 1 and 2 were drawings of preparations cut in paraffin, and stained with polychrome eosin. Magnification 500.

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